THE AMERICAN JOURNAL of HUMAN GENETICS

VOLUME 5 *September 1953* NUMBER 3

Published Quarterly by

THE AMERICAN SOCIETY OF HUMAN GENETICS

THE AMERICAN JOURNAL OF HUMAN GENETICS

is a quarterly record of research, review and bibliographic material relating to heredity in man, and to the applications of genetic principles in medicine, anthropology, psychology, and the social sciences. It is owned and controlled by the American Society of Human Genetics, and is edited by a staff appointed by its Board of Directors.

Subscription, per volume, $8.00 *Single numbers*, $2.50

THE American Journal of Human Genetics is published quarterly at Baltimore, Md. in March, June, September, and December. A volume will consist of four numbers, totaling approximately 400 pages. Subscription and other business communications should be addressed to the publishers, The American Society of Human Genetics, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, or to the Treasurer, Dr. C. Nash Herndon, Department of Medical Genetics, Bowman Gray School of Medicine, Winston-Salem, North Carolina, U.S.A. Remittance for subscriptions from countries other than the United States must be payable in U. S. currency or its full equivalent. Checks or money orders should be made payable to the American Society of Human Genetics.

The American Journal of Human Genetics

Vol. 5 No. 3 *September 1953*

Regular Two-Allele and Three-Allele Phenotype Systems[1]

Part I

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1. INTRODUCTION

THE PRINCIPAL ELEMENTS of formal genetic theory might be said to consist of (1) chromosomes, (2) genes, (3) genotypes, and (4) phenotypes. One branch of genetics, sometimes called phenogenetics, or, more commonly, physiological genetics, is primarily concerned with the connections or relations between (3) and (4). Considering the complexity of this field, it is somewhat surprising that the geneticist's special vocabulary for describing genotype-phenotype relations has remained as simple as it is. Genetical glossaries, in fact, contain only a few terms which have been devised for describing a system of correspondences between a set of genotypes and a set of phenotypes. Two terms, penetrance and expressivity, are used to denote irregular or variable expressions of genotypes. Two additional terms, epistasis and hypostasis, are concerned with non-additive phenotypic effects of genotypes at different gene loci. If we confine our attention to *regular* or non-varying expressions of genotypes at a single locus, we are then forced to rely largely on a single term, *dominance*, together with its converse, recessivity, and certain derived compounds such as partial dominance, semi-dominance, mosaic dominance, over-dominance, co-dominance, and the like.

In a somewhat restricted sense the present outline is concerned with some logical difficulties in extending this 'nomenclature of dominance' to the important class of problems which involve *multiple alleles*. Some prodromal symptoms of these difficulties are apparent even in a consideration of the 'regular relations' which can exist in diploid organisms between *two* alleles. The pathology does not become acute, however, until one reaches the case of three or more alleles. The need for a more explicit and flexible terminology then becomes apparent, in much the same way as the common terms for classes of genotypes themselves (homozygote, heterozygote) no longer prove adequate when one passes from the genetics of diploids to the genetics of polyploids.

More broadly stated, the object here is to consider a number of combinatorial

Received April 2, 1953.

[1] Based upon a lecture entitled "The Formal Logic of Multiple Allelic Systems," sponsored by the Genetics Seminar, University of California, at Davis, April 7, 1952. The author wishes to thank Drs. H. W. Norton, C. Stormont and M. M. Green for their helpful discussions and criticisms. Preparation of the manuscript was made possible by financial assistance extended to the University of California bovine blood group research project by the *Purebred Dairy Cattle Association*.

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and nomenclatural questions which arise when we view the general problem of genotype-phenotype relations in its simplest form, i.e. when the phenotypic variation is of a "qualitative" nature, and when the system of correspondences between genotypes and phenotypes is of a form which shall be called a *regular phenotype system*. We may start with a definition of this and related terms.

DEFINITION 1. *A system of correspondences between a set of G genotypes and a set of Φ phenotypes will be called a* **phenotype system**[3] *of* **rank** *G and* **index** *Φ.*

DEFINITION 2. *A phenotype system is* **regular** *if each of the G genotypes corresponds to one and only one phenotype, i.e. if, under any conditions of classification and for any arbitrarily defined population, all individuals of a given genotype exhibit the same phenotype, and if this is true of all genotypes.*

DEFINITION 3. *A phenotype system is a* **completely specified one-locus disomic** *system of* **degree** *m if the G genotypes consist of the entire set of* $\frac{1}{2}m(m+1)$ *genotypes which can be formed from a set of m alleles in the disomic or diploid state.*

Definitions 1 and 2 have been framed in such a way that they might be applied to phenotype systems relative to genotypes at one or more loci and to species possessing such genes in the single, double or multiple state (e.g. monoploids, diploids, polyploids) or to various combinations of these conditions (e.g. monosomics and disomics in the case of sex-linked genes in man). In this outline, however, we shall be concerned solely with *one-locus disomic* systems, e.g., any autosomal locus in man, or any sex-linked locus in the homogametic sex. For brevity's sake, the adjectives 'one-locus' and 'disomic' will be omitted in the following discussion and throughout the paper.

We shall also be concerned exclusively with *regular* and *completely specified* phenotype systems.

Regularity.—The term 'regular' is suggested by the common usage 'irregular dominant' denoting the case in which some individuals heterozygous for a mutant gene are phenotypically abnormal and some are not; in such cases the proportion of abnormal heterozygotes is termed the penetrance of the mutant gene in heterozygotes. Restricting ourselves to systems in which all phenotypic expressions in all genotypes are regular, we shall thus have no need for the terms penetrance and expressivity.

Number of Genotypes.—With respect to any set of m alleles, the total number of conceivable genotypes in disomics (diploids) is $\frac{1}{2}m(m+1)$, this being the number of combinations of m things taken two at a time, with duplications (homozygotes) allowed. In accordance with definition 3, we assume that all $\frac{1}{2}m(m+1)$ genotypes *exist* and that their phenotypes are *known*. The phenotype system may then be

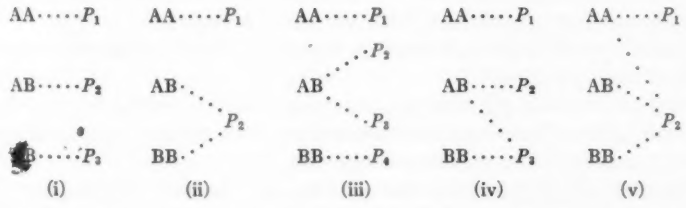
[3] What is here defined as a 'phenotype system' would perhaps be more fully described as a genotype-phenotype system. The shorter designation would seem sufficient, however, since the term 'phenotype' is almost always used in a restrictive sense, referring to observed characteristics associated with a specified genotype. It should be noted that 'phenotype system' does not specify a particular set of phenotypes or a particular set of genotypes, but refers only to the system of correspondences connecting the two. This will be seen most clearly in figures 1 and 3 of sections 2 and 3, where each phenotype system is defined by a diagram in which the genotypes need not be labelled nor the corresponding phenotypes specified.

described as a completely specified m-allele system; since $G = \frac{1}{2}m(m + 1)$ the rank of such a system is fixed by the degree of the system, m. In practice, of course, an m-allele phenotype system may be incompletely specified. In the study of natural populations, one or more alleles may be so rare that some genotypes will not have been encountered, or, if encountered, will not have been recognized. Even in experimental genetics, some genotypes may be unknown, due to infertility of other genotypes which might serve as their parents or due merely to arbitrary limitation of the scope of the breeding experiments. In this outline we shall not be concerned with the classification of phenotype systems relative to such incomplete sets of genotypes. On the other hand, when considering examples of m-allele phenotype systems, m need not represent the total number of alleles known at any locus; if z be the latter number, one can arbitrarily delimit any subset of m alleles ($m < z$) for which all $G = \frac{1}{2}m(m + 1)$ genotypes are known.

Number of Phenotypes.—Definition 2 excludes the possibility of any one genotype corresponding to two or more phenotypes, but does not exclude the correspondence of two or more genotypes to a single phenotype. In other words, in any regular phenotype system the genotype-phenotype correspondences are many-one but not necessarily one-one (many-one and one-many). The number of phenotypes or index of the system, Φ, may therefore take any number from 1 to G.

Gene Symbolism.—For a number of special formulations to be used in this paper it would be inconvenient to employ superscript letters or numerals attached to a single base-letter to designate a set of alleles. Except when citing specific examples, where the symbols of the literature will be used, we shall adopt A, B, $\cdots$ M as symbols for any set of m alleles. The reader is advised to think of these as abbreviated symbols for $V^{\mathrm{A}}, V^{\mathrm{B}}, \cdots V^{\mathrm{M}}$ or any similar set distinguished by the letters A, B, $\cdots$ M. This practice of dropping the base-letter, sometimes used in the literature on blood groups, is of course generally undesirable. It will, however, greatly simplify and clarify various formulae in later sections of this paper, where interest centers on combinatory and permutational considerations. Confusion is hardly possible, since we shall not be concerned with more than one allelic set at a time.

To illustrate the meaning of various terms used in definitions 1–3, we may consider the following set of diagrams depicting some two-allele phenotype systems. The letters A and B stand for two alleles, giving rise to the three genotypes AA, AB and BB. The letters P_1, P_2, P_3 and P_4 denote any four arbitrary phenotypes. Correspondences between genotypes and phenotypes are indicated by broken lines.



All five systems are *completely specified* since the phenotypes are specified for the entire set of $G = \frac{1}{2}m(m + 1) = 3$ genotypes. Systems (i) and (ii) are *regular*, since each genotype

corresponds to only one phenotype, although a given phenotype may correspond to two or more genotypes, as is true of P_2 in (ii). The remaining systems are *irregular*, since each contains at least one genotype corresponding to two or more phenotypes. For example, in (iii) the two lines leading from AB signify that some individuals of genotype AB exhibit phenotype P_2 while others exhibit P_3. System (v) would represent the case of a gene, A, which is "completely recessive" but only irregularly expressed as an abnormality (P_1) even in the homozygous state. In irregular systems, the number of phenotypes may exceed the number of genotypes ($\Phi > G$), as in (iii), whereas in regular systems we must have $\Phi \leq G$.

Examples of *incompletely specified* 2-allele phenotype systems would be illustrated by removing AA from each of the five diagrams; we may designate the five systems thus modified by (i)′, (ii)′, . . . (v)′. System (i)′ would then represent the common case of "provisional dominance," e.g. a rare mutant gene A in man which regularly produces an abnormality (P_2) in heterozygotes, but is unknown in the homozygous state.

DEFINITION 4. *Two regular and completely specified m-allele phenotype systems will be said to be* **permutationally equivalent** *or to be* **images** *of the same* **phenogram** *if they are of the same index and if there exists one or more permutations of the letters* A, B, · · · M, *standing for the m alleles, which transforms the one system into the other; otherwise they will be said to be* **permutationally distinct** *or to belong to different phenograms.*

Definition 4 is perhaps not fully explicit, but its meaning will be made increasingly clear in sections 2 and 3; a fuller statement of the problem will be presented in section 4.

The objects of this outline are to enumerate the phenograms or permutationally distinct regular phenotype systems involving two and three alleles, to consider a variety of nomenclatural questions pertaining thereto, and, whenever possible, to generalize the principles concerning these questions to systems involving any number of alleles.

Definitions 1–4 will be seen to contain two arbitrary or undefined elements: the concept 'phenotype' and the phrase 'conditions of classification'. Were it the desire to consider only the mathematical aspects of the aforementioned problems, these matters might well be left uninterpreted. The author feels obliged to present his own interpretations, however, in order to justify the examples of phenotype systems to be mentioned in the following sections. The discussion may also help to make clear what advantages might be expected to derive from a combinatorial classification of regular phenotype systems, of which the present account must be regarded as forming merely an introductory and very sketchy outline.

The Concept of Phenotype.—As used in this paper, the following points regarding 'phenotype' should be noted:

1. The term is used in the usual way, referring strictly to *observable* characteristics, excluding of course "breeding characteristics" or, more broadly stated, information concerning relatives of the organism in question.

2. Whatever the nature of the observations, it is assumed that the comparison of any two individuals can be significantly described as 'distinguishable' or 'indistinguishable' and that the latter relation is transitive (cf. §5).

3. When two or more "properties" or "traits" are referable to a given genotype, the term phenotype will be understood in Part I of this outline to comprehend the entire complex or syndrome of such traits. Definition 2 therefore requires that all such properties be regularly expressed (observed) in individuals of any given genotype, and that this be true for all G genotypes. It should be noted that regular expression of all properties in all genotypes does not imply a consistent association or dissociation of any two properties for all genotypes. Thus, if the phenotype of any specific genotype be $x+y+$ (presence of properties x and y), the phenotypes corresponding to other genotypes in the system are not restricted to the combinations $x+y+$ and $x-y-$, but may possibly be $x+y-$ or $x-y+$; the only requirement is that no two combinations of properties be manifested in individuals of the same genotype. In this connection it may be remarked that 'dominance' will be employed in this paper as a relation between two alleles, in essential agreement with the following definition due to Feller (1950): "A is *dominant* and a recessive. By this is meant that Aa-individuals have the same observable properties as AA, so that only the pure aa-type shows an observable influence of the a-gene."

Conditions of Classification.—If 'phenotype' refers to *observable* characteristics, it seems clear that factors capable of altering the genotype-phenotype relations (e.g. dominance, penetrance, etc.) might be referable either to the organism *observed* or to the *observer*. Genetics texts stress the importance of modifying genetic and environmental factors as two general categories of the former kind. To the author's mind, a third category which could hardly be considered a part of 'environment' might be recognized under the heading of 'observer factors.' One might be tempted to call them the *human* factors in phenogenetics were it not for the fact that human genetics finds man both in the role of the observer and the observed.

To consider a hypothetical example which places a literal interpretation on the word "observe," one could imagine two alleles, P and p, responsible for pigmentary differences in a certain plant species. To most human observers P and p might lack dominance, all three genotypes being regularly distinguished by eye. To other observers, having a certain form of colorblindness, P might be fully dominant to p, PP and Pp being invariably confused. To still a third set of observers, armed with special colorimetric apparatus or chemical procedures, the system might not only show lack of dominance, but P might prove to be divisible into two sub-alleles, P^1 and P^2. Knowing of these possibilities, one would have to concede that the dominance of P in the second instance depended not so much upon a particular "mode of gene action" in the plant as to a peculiarity—in this case also gene-controlled—of the observer. While possibilities of this kind might seem absurdly trivial, it is evident that there are many other forms of "blindness" which may afflict observers but which may be on occasion—as in the case of P^1 and P^2—overcome, with resulting changes in the genotype or phenotype system. Human geneticists will call to mind numerous instances in such diverse fields as neurology, ophthalmology, hematology and internal medicine, where the ability to discriminate between two genotypes has undergone progressive changes through new discoveries and diagnostic refinements.

Perhaps in no other field are the observer factors more conspicuous than in the study of blood groups in man and other animals. Mainly through acquisition of new

antisera, but also through other changes in technique, the serologist's phenotype and genotype systems have a tendency to evolve fairly rapidly from the simple to the complex. Reverse changes can occur, however, when the supply of a particular antiserum becomes exhausted and proves irreplaceable, or when, for other reasons which need not be wholly arbitrary, the serologist employs a scheme of classification other than the most discriminatory one known to or available to him. Concerning one situation of this kind in human blood group research, Race and Sanger (1950) remark: "Had anti-*d* been discovered first, then *d* would have appeared to be a dominant character; and the moral of this is that it is wiser to avoid using the words dominant and recessive in relation to *Rh*. With the possible exception of the *Lewis* system, this caution may be extended to all blood groups."

The problem mentioned here seems important to the present discussion in a number of ways. In the first place, a misunderstanding seems avoidable if one agrees to include the 'observer factors' among those for which some degree of uniformity must often be specified if the phenotype system can be expected to be regular. The phrase 'conditions of classification' in definition 2 is intended to suggest conditions referable both to the observed organism and the observer. The phenotype system, and hence any terms used to describe it such as 'dominance', will be regarded as not necessarily fixed or regular even when, as is commonly true in serological or biochemical genetics, the variations due to modifying genetic and environmental factors are negligible. On this view, then, we would not hesitate to say—to take an example paralleling that mentioned above—that the Kell-antigen gene *K* was indeed dominant to *k* when anti-*K* serum alone was available, but that *K* ceased to be dominant when anti-*k* was discovered and was used jointly with anti-*K*.

Yet, even if we accept 'dominance' and 'lack of dominance' with this understanding—requiring of these terms only that they describe the phenotype system achieved under any set of conditions sufficiently uniform to insure regularity—we shall find that they are generally inadequate for this purpose if the system is one involving *multiple* alleles. For example, suppose that a collection of bloods is tested *uniformly* with anti-A, anti-B, anti-M and anti-N sera. With respect to the M–N classifications, the phenotype system is regular and its essential features are fully described by saying that we are dealing with two alleles lacking dominance. The phenotype system for ABO is also regular, presenting four phenotypes, but it is *not* unambiguously or uniquely defined by the usual statement: genes L^A and L^B lack dominance with respect to each other, but both L^A and L^B are dominant to a third allele *l*. Actually, as we shall see in section 6, it is the 'lack of dominance' rather than dominance which introduces ambiguity in the statement. This kind of defect seems to the author a much more serious one limiting the usefulness of the terminology of dominance in those fields of genetics where complex allelic or pseudo-allelic systems are the rule.

But, while we may seek to preserve for 'dominance' a wider applicability in this way, one must admit of real difficulties in the varying connotations of 'dominance' in different fields of genetics. The physiological geneticist may readily agree that relations such as dominance or penetrance are often liable to extreme modification through changes in the genetic background or environment, but he might find it

anomalous to think of these relations as referring in some cases almost wholly to the resourcefulness, the diagnostic and sensory equipment, or even the whims of human observers. One wonders, however, where one could draw a line if the caution of Race and Sanger were to be extended to other fields of genetics. Is there indeed any field in which an inability to distinguish phenotypically between AA and Aa can be axiomatically accepted as a permanent state, implying either that the gene substitution is wholly without effect, or that such effect, if it exists, must necessarily remain undiscovered?

However this question may be answered, it would seem that the geneticist's first need is for a terminology which describes, as concisely and unambiguously as possible, what is *actually accomplished* in differentiating a set of genotypes, without necessarily implying anything about gene actions or interactions or about consequences of the phenotypic differences to the organism observed. This is so because it is the phenotype system achieved, rather than any other one theoretically possible, which determines such "practical" applications as the following:

a) The probability of discovery of the genotype system under any conditions of gene frequency ratio, mating system, mutation, selection, etc.;

b) The gene frequency estimation equations and other statistical methods needed for the analysis of population or family data;

c) The kinds of eugenic predictions which the human geneticist may make, or of breeding programs which the animal geneticist may adopt;

d) The kinds and frequencies of successful medico-legal applications which the genotype system affords; etc.

From a list of this kind, it will be clear why the problem of genotype-phenotype nomenclature is of greater concern to the human geneticist than to the experimental geneticist. Consider the leaf pigmentation alleles P, p^G and p in Coleus, which, as shown by Boye (1941), present the following genotype-phenotype correspondences:

Pp^G	grey
PP and Pp	purple
p^Gp^G and p^Gp	green
pp	pattern

Under the usual experimental opportunities granted to the plant geneticist, Dr. Boye required no special set of statistical methods in establishing this theory, nor were applications of sorts (*c*) and (*d*) in view. Interest centered therefore on matters of physiological interpretation, rather than on the statistical manifestations of such a system in natural populations of Coleus.

By contrast, when Bernstein in 1925 proposed essentially the same three-allele phenotype system in explanation of the four blood groups, O, A, B and AB, special statistical procedures had to be devised for testing the hypothesis in relation to population and family data. In fact, an extensive mathematical literature has accumulated relative to this particular 3-allele 4-phenotype system, and such theory and methods are now available for any similar problem arising in human genetics or elsewhere. But, because the terminology of dominance proves inadequate, we have at present no better means of referring to this class of problems than to say

'those 3-allele phenotype relations which are like the O-A-B-AB system of human blood groups.'

With but a few exceptions, each phenogram or permutationally distinct phenotype system to be described in sections 2 and 3 of this paper will have its own statistical laws and regularities, which will have to be elaborated as such problems arise in the study of human genetics. A first desideratum would seem to be to have a concise means of identifying such systems, especially the simpler ones involving two or three alleles. Being based upon the entire field of combinatory possibilities, such a nomenclature might be expected to help systematize the study of the statistical properties of such systems. Also, being free of connotations concerning gene functions which may sometimes attach to such overburdened terms as dominance, the physiological geneticist might find herein a useful auxiliary nomenclature.

2. REGULAR TWO-ALLELE PHENOTYPE SYSTEMS

Given two alleles, A and B, forming three genotypes, there are only 5 ways in which the genotypes can be grouped in such a way as to give rise to any number, 1 to 3, of phenotypes. These possibilities are easily pictured by representing the genotypes as small circles or dots arranged in the form of an equilateral triangle (fig. 1). An open circle (o) is used to symbolize the heterozygote, AB, while filled circles or dots (●) are used for the two homozygotes, AA and BB. A heavy line or 'identity bar' (—) is then used to connect any two genotypes which are assumed to be identical with respect to phenotype. Unconnected dots or circles therefore signify genotypes which are phenotypically distinguishable.

The beginning student of heredity is early made familiar with the fact that 'dominance' and 'recessivity' are not complementary relations, which is to say that if A is not dominant to B, it is not necessarily true—even assuming a regular system—that A is recessive to B. A third possibility, commonly referred to as the case of 'no dominance', is depicted by the first triad of genotypes in figure 1. Here the *two* alleles produce genotypes corresponding to *three* phenotypes, and there is but *one* way in which this can come about; we shall therefore designate this system as phenogram 2-3-1. In general, the symbol will be m-Φ-n, where m is the degree of the system (number of alleles), Φ is the index (number of phenotypes), and n is a serial number made necessary by the fact that there is often more than one phenogram having a specified degree and index.

The case of 'dominance' is represented in figure 1 by two diagrams which together are designated as phenogram 2-2-1. This is the first example of what the author has chosen to call 'permutational images' of a single phenogram. The two diagrams are configurationally similar, and the one is converted into the other upon transposition of the letters A and B. It is, of course, an arbitrary matter whether any two alleles be labelled A and B or vice versa. This is not to say that it is a matter of indifference whether any particular *phenotype*, e.g. a rare human abnormality, be inherited as a 'dominant' or as a 'recessive'; the two have very different "genetic behavior." Nevertheless, an understanding of the statistical properties of phenogram 2-2-1 throughout the entire range of possible gene frequency ratios, comprehends an understanding of both the rare dominant and the rare recessive; and in this sense

2-2-1 presents a single system for study. On the other hand, we are not uninterested in the fact that two permutational images of 2-2-1 exist, and this will be appreciated, among other ways, when we come to consider 'dominance' relations among three or more alleles. In general, we are interested equally in the numbers of distinct systems or phenograms and in the numbers of their permutational images.

Now, contrary to what one might logically infer from the expressions 'dominance' and 'no dominance,' these two systems do not exhaust the possible regular phenotype systems for two alleles. There are two remaining possibilities, designated in figure 1 as 2-2-2 and 2-1-1. The former presents two phenotypes, one of which is peculiar to the heterozygote (AB) alone, the two homozygous classes being indistinguishable. Although examples of this system are known in various fields of genetics (cf. §§5, 7), there seems to be no serviceable name for it, so that we shall refer to it momentarily as the 'unnamed system.'

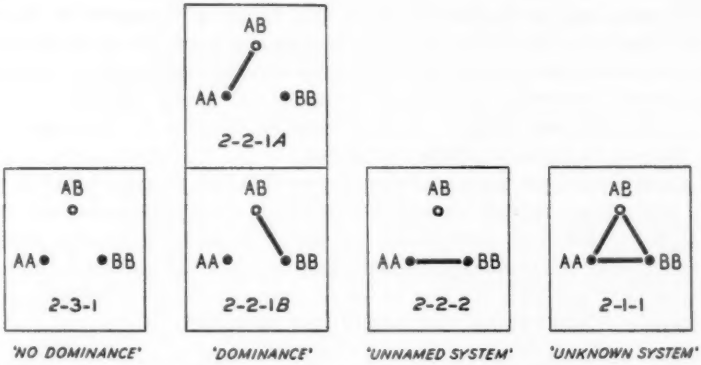


FIG. 1. The 4 two-allele phenograms, one of which—'dominance'—exhibits two permutational images.

Phenogram 2-1-1 will be called the *identity system* or 'unknown system,' since, if all genotypes have the same phenotype, there is nothing to bring the system to light. Obviously, for any value of m there will be one identity system, m-1-1. One could consider such cases as 'improper' and omit them in any enumeration of systems, but the author prefers not to do so. Geneticists will have no difficulty in imagining genes with unknown effects. But, more significantly, the 'unknown' system may become 'known' in two general ways. One of these consists in the discovery of new 'conditions of classification;' for example, the M and N blood-group genes in man might be said to have formed system 2-1-1 prior to 1927, when Landsteiner and Levine's production of anti-M and anti-N antibodies changed the system to 2-3-1. Yet even if the three genotypes MM, MN and NN were to remain—under all observational techniques—indistinguishable *inter se*, the existence of the two genes M and N might still be inferred if there should be discovered an additional allele, say Q, giving phenotypically distinguishable heterozygotes with M and N. Thus, any identity system, m-1-1, may become recognizable though incorporation into

certain systems of degree $m + 1$ or higher, as will be discussed more fully in section 6. It therefore becomes expedient not only to recognize 2-1-1 as a theoretical case but also to have a designation for such relation between A and B when a 'triangular' system of phenotype identities of this kind is encountered in systems of 3 or more alleles.

Some Statistical Properties of Phenogram 2-2-2

From the definition of a phenogram (§1, definition 4) it seems obvious that no two phenograms will generally (i.e. throughout the entire range of population frequency ratios or under any conceivable system of controlled breeding tests) exhibit the same "genetic behavior" or, in other words, the same statistical properties in relation to population data and family data. In section 6 we shall note an exception to this principle, which, however, seems trivial.

The principle is easily demonstrated for the four 2-allele phenograms. The cases of 'dominance' and 'no dominance' are so well known as to require no discussion, and the identity system (2-1-1) leaves us nothing to discuss. The problem therefore reduces to showing that, at least under favorable experimental breeding opportunities or population frequencies, system 2-2-2 should be readily distinguishable from 2-2-1 or 2-3-1. We shall mention here a few peculiarities of the 'unnamed system' which trace to its unusual symmetric features.

Let p and q stand for the population frequencies of two alleles, A and B, respectively, and assume random mating with a simple equilibrium genotype ratio p^2 AA:$2pq$ AB:q^2 BB. For convenience, we will write $pq = \theta$. Assume phenogram 2-2-2 and let H be the phenotype corresponding to AB, h representing the alternative phenotype. The expected frequencies of the various classes of matings and the proportions of H and h among their progeny are as follows:

Matings	*Parental Genotypes*	*Mating Frequency*	*Offspring* H	*Offspring* h
$H \times H$	AB × AB	$4\theta^2$	½	½
$H \times h$	AB × AA AB × BB	$4\theta(1 - 2\theta)$	½	½
$h \times h$	AA × BB	$2\theta^2$	1	0
	AA × AA BB × BB	$1 - 4\theta + 2\theta^2$	0	1

Thus, at all gene frequency ratios, all matings with one or both parents of type H would produce H and h offspring in a 1:1 ratio, while matings of two h individuals would always produce all H or all h offspring. The system would therefore be easily distinguished from 2-2-1 or 2-3-1, unless matings of the types AB × AB and AA × BB were both very rare or non-existent. The latter condition would, of course, be expected when either p or q was very small, or when infertility of heterozygotes prevented the production of one of the two homozygotes. When AA is normal, AB

regularly abnormal, and BB unknown, the phenotype system, if regular, could conceivably be 2-3-1, 2-2-1 or 2-2-2, and this is the situation with respect to almost all rare "dominant" abnormalities in man. However improbable it might seem, BB might be entirely normal in phenotype, in which case B could be described as an "abnormal" gene only in the sense of its being the rarer of the two alleles.

At the opposite extreme, when $p = q = \frac{1}{2}$, we have $1 - 4\theta = 0$, so that matings of like and unlike homozygotes now have equal expected frequencies. Hence, when the two phenotypes are equally frequent in the general population, we would expect to find a 1:1 ratio of H and h among the aggregated progenies of matings of all three phenotypic classes, i.e. $H \times H$, $H \times h$ and $h \times h$. This is to say that phenogram 2–2–2 has the peculiarity of showing *no phenotypic association between parents and offspring* when the two phenotypes occur in a 1:1 ratio in a random breeding population. However, they could hardly escape recognition as hereditary traits owing to the heterogeneous results of $h \times h$ matings, half of these producing all H offspring and half producing all h offspring. In general, the parent-offspring and sib-sib association tables would appear as follows:

Parent-offspring Pairs

	H	h	
H	θ	θ	2θ
h	θ	$1 - 3\theta$	$1 - 2\theta$
	2θ	$1 - 2\theta$	

Full Sib Pairs

	H	h	
H	$\theta + \theta^2$	$\theta - \theta^2$	2θ
h	$\theta - \theta^2$	$1 - 3\theta + \theta^2$	$1 - 2\theta$
	2θ	$1 - 2\theta$	

It may be noted that system 2-2-2 offers no opportunity for exclusions of paternity (or maternity) of the two kinds commonly accepted in medico-legal decisions. Thus system 2-3-1 permits unconditional exclusions of paternity as well as exclusions of paternity which are conditional upon the acceptance of maternity, while system 2-2-1 permits only the latter class of exclusion (cf. Cotterman, 1951). System 2-2-2 would, however, afford exclusions which are conditional upon the acceptance of a more complicated set of relationships. For example, if two individuals of phenotype h were accepted as the parents of a child of phenotype h, then any additional child of phenotype H, if assumed to have the same maternity, could not have the same paternity.

One sometimes meets with the expression "to distinguish between alleles." When this phrase is used in reference to the phenotypes of haploids (monosomics, hemizygotes) or in reference to the "tested gametes" of a diploid organism, the meaning may be perfectly clear. Often, however, the expression is used in reference to diploids as a means of avoiding a more complicated statement concerning the distinguishability of genotypes. Here ambiguities are apt to arise, and system 2-2-2 offers a case in point. One possible interpretation might be this: we could say that a regular 2-allele phenotype system permits the distinguishing of the two alleles if each and every phenotype in the system allows us to infer at least one gene in the genotype.

Obviously this is true for the case of two alleles without dominance (2-3-1) and for two alleles with dominance (2-2-1), but not for the system 2-2-2. In H individuals we can infer the presence of one gene of each type, i.e. AB, but in individuals of phenotype h neither gene can be specified, although we can assert that the individual is homozygous.

Another interpretation might be this: we could say that a system permits the distinguishing of two alleles if a unique solution of the two gene frequencies is afforded by a random sample of unrelated individuals drawn from a population having a simple Hardy-Weinberg genotype equilibrium. This criterion seems much like the first, but is actually quite distinct when $m > 2$ (cf. §§4, 6). Here again, however, the system 2-2-2 does not qualify. If $\bar{H}$ stands for the observed proportion of H individuals in the sample, the equation of estimation $\bar{H} = 2p(1 - p)$ has two roots,

$$p = \tfrac{1}{2} \pm \tfrac{1}{2}\sqrt{1 - 2\bar{H}},$$

either of which is admissible. For example, if we knew that a sample contained 42 per cent individuals of blood type MN (MM and NN being assumed indistinguishable), we could take as the estimated proportion of M genes either 0.70 or 0.30.

But, although the two alleles in system 2-2-2 are thus, in some senses, indistinct of unidentifiable, the system itself, and hence the existence of the two genes, can be easily inferred under a wide range of population frequencies. And ideally, under various systems of controlled breeding tests, any sample containing the three genotypes, AA, AB and BB, could be precisely separated into these classes, although any naming of the two homozygous classes would be quite arbitrary.

3. REGULAR THREE-ALLELE PHENOTYPE SYSTEMS

Summarizing the situation for two alleles, we may say that 'dominance' and 'no dominance' fairly well take care of the regular phenotype systems commonly encountered, leaving unnamed only one system, 2-2-2, which is without doubt a rare kind of "interaction," plus, of course, the identity system, 2-1-1, which might seem to deserve no recognition in any nomenclature. When we turn to the case of three alleles, however, the terminology of dominance seems hopelessly outclassed, since there are now 52 distinct three-allele phenotype systems, but only 7 ways in which these could be described exclusively in terms of 'dominance' and 'lack of dominance.'

To represent the six genotypes derived from three alleles, we now arrange 6 dots and circles in the form of a regular hexagon, the 3 heterozygotes alternating with the 3 homozygotes in such a way that each heterozygote is located at a vertex adjacent to and midway between its two 'parent-homozygotes,' e.g. AB between AA and BB. The familiar case of multiple allelic inheritance of albinism, Himalayan and self-color in the rabbit can then be summarized as shown in figure 2.

Other hexagonal arrangements of the six genotypes are possible, and these are instructive for some purposes which, however, will not be considered in this paper. The arrangement shown in figure 2 will be called the *standard* arrangement.

The 52 three-allele phenograms are displayed in figure 3. This set of diagrams

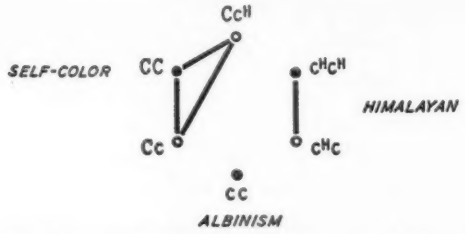


FIG. 2. Genotype-phenotype relations for three pigmentation factors in the rabbit

deserves careful study from several points of view. It will be noted that the 52 systems are arranged, firstly, on the basis of index, i.e. number of phenotypes, Φ. There is only one phenogram having $\Phi = 6$, four having $\Phi = 5$, sixteen having $\Phi = 4$, twenty-one having $\Phi = 3$, nine having $\Phi = 2$, and one—the identity system —having $\Phi = 1$. The numbering scheme used in figure 3 is that previously described, namely m-Φ-n, but the degree, $m = 3$, has been omitted throughout.

Within sets of phenograms having the same index, the systems are further subdivided on the basis of the *partitional specification*, i.e. the numbers of genotypes entering into the various subsets having the same phenotype. This is first illustrated for $\Phi = 4$, where the first ten diagrams depict the genetically distinct systems having phenotypes comprising, respectively, 2, 2, 1, 1 genotypes. These ten are followed by six diagrams exhibiting a triangular configuration of identity bars, indicating the partition 3, 1, 1, 1. In treatises on combinatory analysis, these partitional specifications are usually shortened to $2^2 1^2$ and 31^3; there is no further possibility for 6 things partitioned into 4 parcels. For $\Phi = 3$, we have partitions 2^3, 321 and 41^2, and for $\Phi = 2$, we have 3^2, 42 and 51; these subdivisions are easily recognized in figure 3.

In phenograms 3-5-1, 3-5-2, 3-5-3 and 3-5-4 we have displayed the four kinds of identity couplets or genotype pairings which can be constructed in a 3-allele system, *viz.* couplets of the sorts AA—AB, AB—AC, AA—BB, and AA—BC. That these give rise to four distinct systems is apparent from the fact that no permutation of the letters A, B and C would transform any one of these couplets into the other. The same principle applies to phenograms of indices 4, 3, 2, and so a further ordering of the 52 diagrams has been effected, making use of the various combinations of these four kinds of couplet. However, no very useful purpose is served by the last two forms of systematization, and we must therefore regard the number n in m-Φ-n as an arbitrary serial number. One could consider a variety of more elaborate and more revealing schemes for numbering these 52 systems, but the present one will serve our needs.

The notion of equivalent systems also takes on added complexity in passing from the case $m = 2$ to $m = 3$. In two-allele systems, a particular phenogram was either asymmetric (2-2-1) and exhibited two permutational images, or it was symmetric (2-3-1, 2-2-2, 2-1-1) and possessed a single image upon transposition of A and B. With three alleles, the permutations of A, B and C form the symmetric group of order 6:

$$P_3\text{: } I, \text{(ABC)}, \text{(ACB)}, \text{(AB)}, \text{(AC)}, \text{(BC)}$$

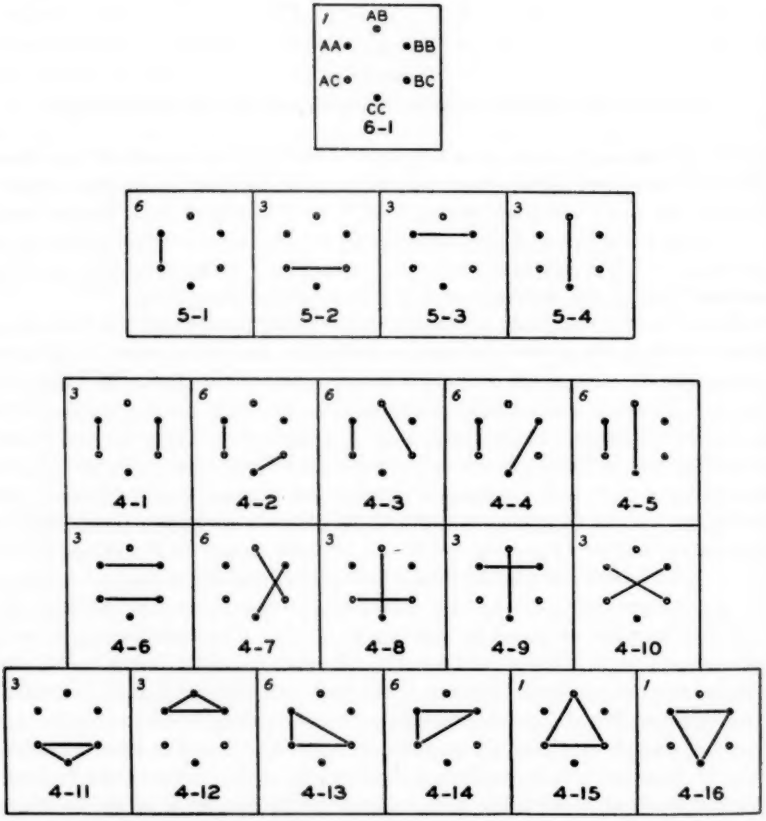
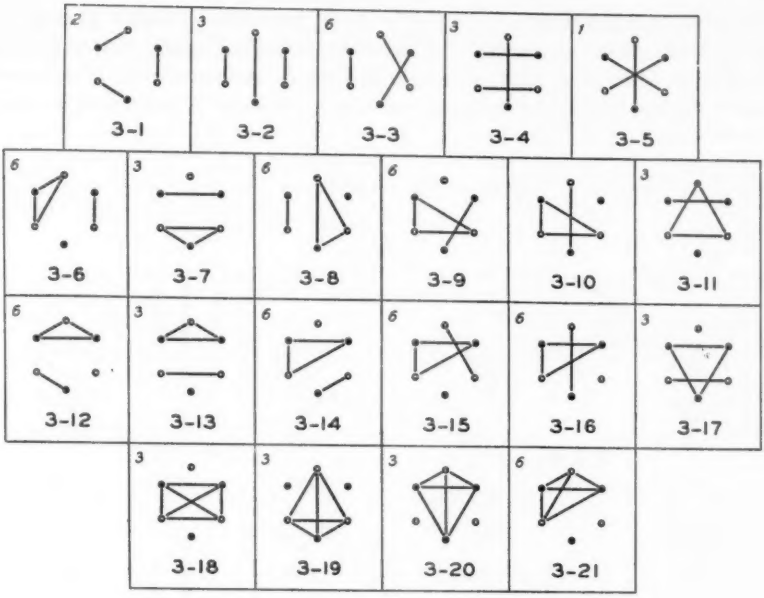
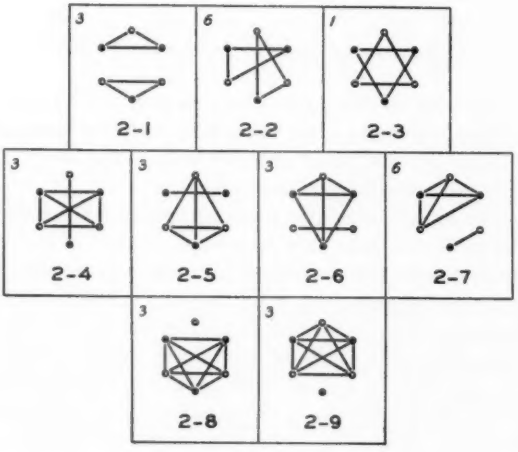


FIG. 3. The 52 three-allele phenograms, arranged according to number of phenotypes and partitional specification. The number of permutational images is indicated in the upper left corner of each diagram. (Figure is continued on opposite page.)


2
3-1
3
3-2
6
3-3
3
3-4
1
3-5
6
3-6
3
3-7
6
3-8
6
3-9
3-10
3
3-11
6
3-12
3
3-13
6
3-14
6
3-15
6
3-16
3
3-17
3
3-18
3
3-19
3
3-20
6
3-21


3
2-1
6
2-2
1
2-3
3
2-4
3
2-5
3
2-6
6
2-7
3
2-8
3
2-9


1
1-1

wherein the permutations are written in cyclic form. Many 3-allele phenograms, such as 3-3-6, exhibit no symmetry of any kind and under permutation of A, B and C form a set of 6 images which is isomorphic with P_3 considered as a "homogeneous space."[4] Others, like 3-3-2 (cf. fig. 4), are symmetric about a single axis, so that a

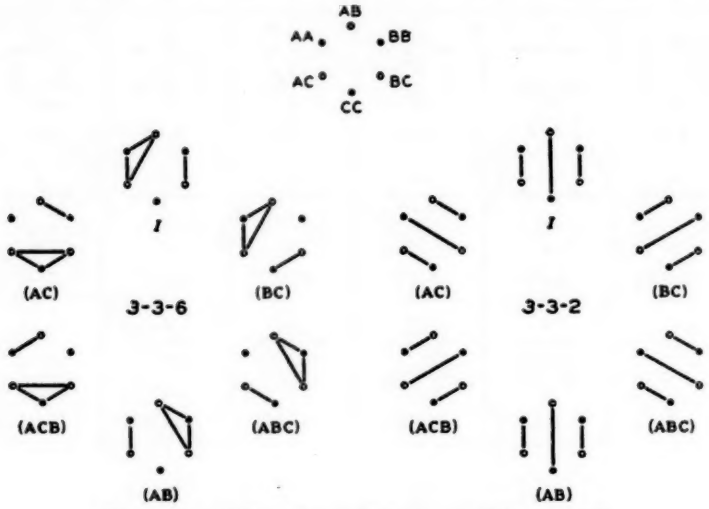


FIG. 4. Permutational images of phenograms 3-3-6 and 3-3-2

simple transposition, such as (AB), leaves the image of 3-3-2 unchanged; there are therefore only 3 images, forming a set isomorphic with the homogeneous space of P_3/H_{AB}, i.e. the set of left-cosets of P_3 relative to H_{AB}, the latter consisting of the identity element (I) and the transposition (AB).

There are two remaining possibilities. One phenogram, 3-3-1, is asymmetric about all three axes, but exhibits a cyclic symmetry upon rotation of the diagram through 120 degrees; it therefore has but two images, forming a set isomorphic with P_3/A_3, where A_3 is the alternating subgroup, consisting of I, (ABC) and (ACB). Finally, there are 6 phenograms which are symmetric in all respects, and these therefore have a single image, isomorphic with P_3/P_3. In general, the images of any m-allele phenogram will form a set which is homomorphic with the homogeneous space of P_m, which means that P_m will contain one or more permutations corresponding to a given image of the phenogram, depending on the various kinds of symmetry displayed by the latter.

At the moment we are interested in the numbers of permutational images of the various three-allele phenograms as a means of verifying the completeness of

[4] This is a technical term of mathematics used to describe the structure of an abstract set which is "acted on" by a group in a definite way. The isomorphisms referred to concern this "homogeneous structure." The other terms used in this and the following paragraph are explained in standard texts on the theory of finite groups (e.g. Ledermann, 1949).

our catalogue of 52 such systems. If we add together the numbers of images for all phenograms (cf. fig. 3), we obtain, for the total number of 3-allele systems, 203. This number is well-known to students of combinatorial analysis: it is simply the number of "equivalence relations" or partitions (into subsets of any size) on a set of 6 elements. The general formula is given in section 4. The enumerations can be performed separately for systems of any given index or partitional specification, and, on comparison with the numbers of permutational images for the corresponding phenograms, we obtain the summary shown in table 1.

TABLE 1. NUMBERS OF 3-ALLELE SYSTEMS AND 3-ALLELE PHENOGRAMS, CLASSIFIED BY INDEX AND PARTITIONAL SPECIFICATION

INDEX (NO. OF PHENOTYPES) Φ	PARTITIONAL SPECIFICATION $\Pi(p^a)$	NUMBER OF PHENOGRAMS $n_{m\cdot\Phi}$	NUMBER OF PHENOGRAM PERMUTATIONS $N_{m\cdot\Phi}$
6	1^6	1	1
5	21^4	4	15
4	2^21^2	10 } 16	45 } 65
	31^3	6	20
3	2^3	5	15
	321	12 } 21	60 } 90
	41^2	4	15
2	3^2	3	10
	42	4 } 9	15 } 31
	51	2	6
1	6	1	1
Totals		$n_3 = 52$	$N_3 = 203$

4. REGULAR m-ALLELE PHENOTYPE SYSTEMS

As already noted, the total number of genotypes possible in the case of m allelic genes is $G = \frac{1}{2}m(m+1)$. We shall let $N_{m\cdot\Phi}$ stand for the total number of m-allele phenotype systems (counting the permutational images of all phenograms) wherein the G genotypes combine into exactly Φ phenotypes. This number is readily provided by Cauchy's formula for the number of partitions of G identifiable (all-different) objects into Φ indifferent (unordered) parcels, of which a_i parcels contain exactly p_i objects,

$$N_{m\cdot\Phi} = \sum_{p/a} \left\{ \frac{G!}{\prod (p_i!)^{a_i} a_i!} \right\}, \quad \text{where} \quad \sum a_i p_i = G, \quad \text{and} \quad \sum a_i = \Phi.$$

Here summation over 'p/a' means that $(p_1^{a_1} p_2^{a_2} \ldots)$ is what is called an additive partition of the integer G into Φ parts, written in the standard way of the 'partitional

specification' mentioned earlier. Numerical values of $N_{m\cdot\Phi}$ are given in table XXII of Fisher and Yates (1943) for values of G from 2 to 25 and for values of Φ from 2 to G. Summing this over all values of Φ from 1 to G, we get the total number of m-allele phenotype systems of all indices, which we may denote by N_m.

Similarly, we shall denote by $n_{m\cdot\Phi}$ the number of phenograms of degree m and index Φ, and by n_m the total number of phenograms of all indices ($\Phi = 1, 2, \cdots G$). The problem of specifying $n_{m\cdot\Phi}$ and n_m is considerably more complicated than that of specifying $N_{m\cdot\Phi}$ and N_m, and so far the author has not been able to reach any useful formula for simplifying these enumerations. It seems of interest to state the problem here, in both abstract and genetic phraseology, in order to amplify definition 4 of section 1.

We have a set of m identifiable (all-different) objects (alleles), A, B, $\cdots$ M, the permutations of which form the symmetric group $\boldsymbol{P}_m$ of order $m!$. We construct two derived sets of paired objects (genotypes) denoted by

$$\mathfrak{G}_1\text{: AA, BB, } \cdots \text{ MM;}$$

and

$$\mathfrak{G}_2\text{: AB, AC, } \cdots \text{ LM;}$$

(the m homozygotes and $\frac{1}{2}m(m-1)$ heterozygotes, respectively). We then partition the whole of these genotypes into Φ subsets (phenotypes) without restriction as to the composition of the subsets with respect to elements of $\mathfrak{G}_1$ and $\mathfrak{G}_2$; no subset is empty, and each genotype occurs in only one subset. The genotypes comprising any subset (phenotype) are considered to be unordered, as are the subsets themselves. Each such assemblage of subsets of $\mathfrak{G}_1$ and $\mathfrak{G}_2$ is called a system S of degree m and index Φ. Now, each S is itself an element of a set $\mathfrak{S}$ which is invariant under permutation of the m alleles, $\mathfrak{S}$ being homomorphic with $\boldsymbol{P}_m$ considered as a homogeneous space. The problem is to specify the number $n_{m\cdot\Phi}$ of $\mathfrak{S}$-sets (phenograms) having a specified index Φ, and, by summation over values of Φ from 1 to $\frac{1}{2}m(m+1)$, to determine the total number of m-allele phenograms, n_m.

When $m = 2$ or $m = 3$, it is easy to inspect diagrams of the sorts shown in figures 1 and 3 to ascertain whether any two regular phenotype systems are equivalent, i.e. whether they belong to the same phenogram. When $m \geq 4$, it is more convenient to use a linear representation of the systems, placing in brackets the symbols for genotypes having the same phenotype. For example, consider the following 4-allele systems having $\Phi = 5$:

$$S_1 = [\text{AA AB AC BC}]\ [\text{BB BD}]\ [\text{CC CD}]\ [\text{AD}]\ [\text{DD}],$$

$$S_2 = [\text{CC AC AD CD}]\ [\text{DD BD}]\ [\text{AA AB}]\ [\text{BB}]\ [\text{BC}].$$

Both systems consist of $42^2 1^2$ partitions of ten genotypes. Moreover, the phenotype parcels have identical compositions with respect to the numbers of homozygous and heterozygous genotypes. To show that the two systems are equivalent, we perform the cyclical permutation (ACDB) in S_1, obtaining

$$S_1 \equiv [\text{CC CA CD AD}]\ [\text{AA AB}]\ [\text{DD DB}]\ [\text{CB}]\ [\text{BB}].$$

Now, the order in which two alleles are represented in a heterozygous genotype is immaterial, as is also the order of genotypes within parcels (phenotypes), and the order of the parcels themselves. Making these three kinds of rearrangement, we see that

$$S_1 \equiv [CC\ AC\ AD\ CD]\ [DD\ BD]\ [AA\ AB]\ [BB]\ [BC] = S_2.$$

On the other hand, the following systems, having $m = 4$ and $\Phi = 4$,

$$S_3 = [AA\ AB\ AC]\ [BB\ BD\ DD]\ [AD\ CD\ BC]\ [CC],$$

$$S_4 = [BB\ BC\ CD]\ [AA\ AD\ DD]\ [AB\ AC\ BD]\ [CC],$$

likewise have identical partitional specifications and similar parcel compositions, but they are distinct, since none of the 4! permutations of A, B, C and D transforms S_3 into S_4.

Since any particular phenogram of degree m can have at most $m!$ permutational images, a lower bound on the total number of m-allele phenograms is expressed by the inequality

$$n_m > \frac{N_m}{m!}, \quad \text{if} \quad m > 1.$$

Thus, knowing (from the table of Fisher and Yates) that $N_2 = 5$, $N_3 = 203$, $N_4 = 115{,}975$, and $N_5 = 1{,}382{,}958{,}545$, we see that $n_2 > 5/2$, $n_3 > 203/6$, $n_4 > 115{,}975/24$, and $n_5 > 1{,}382{,}958{,}545/120$. Furthermore, the ratio of the average number of permutational images per phenogram to the maximal number, $m!$, is

$$r_m = \frac{N_m}{n_m m!}.$$

By actual enumeration, we know that $n_2 = 4$ and $n_3 = 52$; hence, $r_2 = 5/8 = 0.625$, and $r_3 = 203/312 = 0.651$. Assuming that r_4 and r_5 also lie in the neighborhood of 2/3, we may guess that there are about 7,000 four-allele phenograms and about 17,000,000 five-allele phenograms. We may summarize these facts in a table:

Number of alleles	*Number of genotypes*	*Number of phenograms*	*Number of systems or phenogram images*
m	G	n_m	N_m
2	3	4	5
3	6	52	203
4	10	*c.* 7,000	115,975
5	15	*c.* 17,000,000	1,382,958,545

This staggering rate of increase in n_m discourages any thought of enumerating the entire set of 4-allele phenograms, and this in itself offers some excuse for the detailed listing of three-allele systems in the preceding section. The case of three alleles, representing by definition the *first* instance of *multiple* allelism, is also the *last* case which could be conveniently surveyed in this comprehensive manner.

Many of the general principles pertaining to m-allele systems will, however, be illustratable by the case $m = 3$, as will be shown in section 6. There is, however, one added complication of importance which arises for the first time when $m = 4$, which will now be mentioned. Given m alleles, forming $G = \frac{1}{2}m(m + 1)$ genotypes, there are

$$\tfrac{1}{2}G(G - 1) = \tfrac{1}{8}(m + 2)(m + 1)m(m - 1)$$

ways in which the genotypes can be compared pairwise. These comparisons fall into 5 classes which are distinct with respect to permutations of gene symbols:

	Class of Comparison	*Number of Comparisons*
Intra-pair comparisons	AA with BB, etc.	$\frac{1}{2}m(m - 1)$
	AA with AB, etc.	$m(m - 1)$
Inter-pair comparisons	AA with BC, etc.	$\frac{1}{2}m(m - 1)(m - 2)$
	AB with AC, etc.	$\frac{1}{2}m(m - 1)(m - 2)$
	AB with CD, etc.	$\frac{1}{8}m(m - 1)(m - 2)(m - 3)$
	Total	$\frac{1}{8}(m + 2)(m + 1)m(m - 1)$

TABLE 2. NUMBERS OF GENOTYPE-PAIR COMPARISONS IN MULTIPLE ALLELIC SETS

NUMBER OF ALLELES, m	CLASS OF COMPARISON					TOTAL
	AA—BB	AA—AB	AA—BC	AB—AC	AB—CD	
2	1	2	0	0	0	3
3	3	6	3	3	0	15
4	6	12	12	12	3	45
5	10	20	30	30	15	105
6	15	30	60	60	45	210
7	21	42	105	105	105	378
8	28	56	168	168	210	630
9	36	72	252	252	378	990
10	45	90	360	360	630	1485

The first two classes of genotype comparisons may be called *intra-pair* comparisons, and it is these alone which are explicitly specified by the usual two-gene relations, such as 'dominance' or 'lack of dominance.' However, no m-allele phenotype system ($m \geq 3$) is uniquely defined unless all of the *inter-pair* comparisons are also specified. There are three classes of such comparisons, of which one (AB, CD) is obviously presented only in systems having $m \geq 4$; numerically this class becomes the largest of the five classes of genotype comparisons in systems having $m \geq 8$ (table 2). In section 2, we noted that some m-allele phenotype systems will have the property that at least one allele of the genotype can be identified in individuals of any phenotype. Obviously this will hold only for systems in which all phenotype identities are restricted to comparisons of the sorts AA, AB and AB, AC. Many of the more complex bovine and human blood group systems, though largely or wholly free of

'dominance' relations, may exhibit phenotype identities of the sorts AA—BC or AB—CD.

Although the 15 genotype comparisons are easily pictured in a hexagonal diagram in the case of three alleles, the geometrical limitations become very severe for $m = 4$, where the number of genotype comparisons is 45. Many of the more commonly encountered 4-allele systems, however, can be conveniently diagrammed by placing the four homozygotes at the vertices of a regular tetrahedron, with the six heterozygotes located midway between their 'parent-homozygotes' on the six edges. Two such diagrams, illustrating the human A_1A_2BO and MNSs blood-group systems,

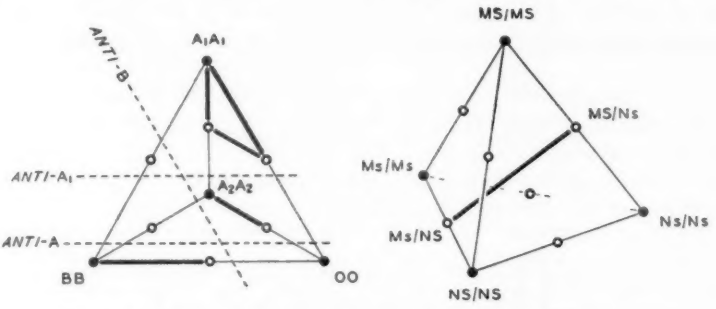


FIG. 5. Genotype-phenotype relations in the A_1A_2BO and MNSs systems

are shown in figure 5. The latter illustrates a system with $m = 4$ and $\Phi = 9$, the single phenotypic identity being of the sort AB—CD.

5. REGULAR TWO-ALLELE RELATIONS

In this section we wish to devise a simple logistic notation for the five regular two-allele systems described in section 2. This will facilitate discussion of the various terms now in use by geneticists for describing genotype-phenotype relations, and will prepare us for section 6, where we shall examine the limitations of such a terminology in connection with phenotype systems arising from multiple alleles.

Dominance is one kind of regular *relation* which may exist between two alleles. The term 'relation' is here used in the logician's sense, referring to "any two- or many-termed predicate" (Woodger, 1937). When we say 'A stands in relation R to B', referring to two alleles, we need not think of any physical, chemical or physiological relations or interactions of the two genes when they occur together in a heterozygote. As already discussed (section 1), relations such as dominance will necessarily depend in part upon conditions other than the intrinsic properties of the genes concerned. Instead, then, 'A stands in R to B' will be understood merely as a brief summarization of the phenotypic correspondences amongst the three genotypes, AA, AB and BB.

We shall use the sign '$\mathfrak{I}$' to stand for *identity with respect to phenotype* and '$\mathfrak{D}$' will stand for the negation of $\mathfrak{I}$, it being understood that the field of these relations is restricted to genotypes at a single gene locus and that the phenotype system is

regular. The signs '$\mathfrak{J}$' and '$\mathfrak{D}$' therefore take the place of presence or absence of the identity bar in the quasi-geometrical scheme used in sections 2 and 3.

Since the concept of 'phenotype' remains essentially undefined, we must take it as axiomatic that $\mathfrak{J}$ is reflexive, symmetric and transitive.[5] Thus, if x, y and z stand for any three genotypes at a single gene locus, we assert, as axioms:[6]

$$x\mathfrak{J}x$$

$$(x\mathfrak{J}y) \equiv (y\mathfrak{J}x)$$

$$(x\mathfrak{J}y.y\mathfrak{J}z) \supset (x\mathfrak{J}z)$$

We shall adopt the following 'gene relation' symbols and designations:

$A \diamond B$	'A is *orthotactic* with B'
$A \rightarrow B$	'A is *dominant* to B'
$A \leftarrow B$	'A is *recessive* to B'
$A \leftrightarrow B$	'A is *metatactic* with B'
$A \rightleftarrows B$	'A is *paratactic* with B'

and these may be defined, using the genotype relations $\mathfrak{J}$ and $\mathfrak{D}$, as follows:

DEFINITION 5.	$A \diamond B \equiv AA\mathfrak{D}AB \,.\, BB\mathfrak{D}AB \,.\, AA\mathfrak{D}BB$
DEFINITION 6.	$A \rightarrow B \equiv AA\mathfrak{J}AB \,.\, BB\mathfrak{D}AB \,.\, AA\mathfrak{D}BB$
DEFINITION 7.	$A \leftarrow B \equiv AA\mathfrak{D}AB \,.\, BB\mathfrak{J}AB \,.\, AA\mathfrak{D}BB$
DEFINITION 8.	$A \leftrightarrow B \equiv AA\mathfrak{D}AB \,.\, BB\mathfrak{D}AB \,.\, AA\mathfrak{J}BB$
DEFINITION 9.	$A \rightleftarrows B \equiv AA\mathfrak{J}AB \,.\, BB\mathfrak{J}AB \,.\, AA\mathfrak{J}BB$

The five definitions are easily seen to correspond to the five regular two-allele systems previously diagrammed (fig. 1). In the definition of '$\rightarrow$' it will be noted that $(AA\mathfrak{J}AB \,.\, BB\mathfrak{D}AB) \supset AA\mathfrak{D}BB$, from the axiom of transitivity of $\mathfrak{J}$; hence, either of the statements $AA\mathfrak{D}BB$ and $BB\mathfrak{D}AB$ could have been omitted, and the same kind of redundancy appears in the last three definitions. However, for the sake of symmetry, all three genotype comparisons have been illustrated here.

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[5] In certain fields of genetics it is possible that the concept of phenotype might be employed in such a way that 'indistinguishability' or identity with respect to phenotype could be non-transitive. For example, if two clones of a microörganism, a and b, were described as having different phenotypes ($\mathfrak{D}$) when they showed a characteristic *interaction* of some kind, but otherwise as having the same phenotype ($\mathfrak{J}$), it could conceivably happen that $a\,\mathfrak{J}\,b$ and $b\,\mathfrak{J}\,c$, but $a\,\mathfrak{D}\,c$. We wish to exclude any 'phenotypes' of this sort.

[6] The logical symbols for negation ($\sim$), conjunction ($.$), the exclusive-or function ($\wedge$), implication ($\supset$), and mutual implication or equivalence ($\equiv$), as used in this paper, are explained in detail by Woodger (1937). Briefly, if **a** and **b** are any two statements, then $\sim$**a** is read '*not*-**a**', **a** . **b** is read '**a** *and* **b**', **a** $\wedge$ **b** is read '**a** *or* **b**, but not both **a** and **b**', **a** $\supset$ **b** is read '**a** *implies* **b**', and **a** $\equiv$ **b** is read '**a** implies **b** and **b** implies **a**'. The sign '$\cap$' will be substituted for '$\wedge$' if **a** and **b** stand for classes (e.g. genotypes) rather than statements.

The five 2-allele relations form a mutually exclusive set. Two of them, 'dominance' and 'recessivity', are *asymmetric*, e.g. $(A \rightarrow B) \supset \sim(B \rightarrow A)$; in fact, each is the *converse* of the other, i.e. $(A \rightarrow B) \equiv (B \leftarrow A)$, which is another way of expressing the notion of permutational equivalence of the diagrams 2-2-1*A* and 2-2-1*B* of figure 1. To complete the analogy with section 2, we shall find it convenient to have a symbol denoting either the relation of 'dominance' or 'recessivity':

DEFINITION 10. $A \uparrow B \equiv (A \rightarrow B) \wedge (A \leftarrow B)$.

The remaining three relations are *symmetric*, and this explains the choice of the signs '$\diamond$', '$\leftrightarrow$' and '$\rightleftharpoons$'. Arrow-like symbols were adopted in preference to letters in order that the relations between several alleles could be pictured in a 2-dimensional network, as will be illustrated in section 6.

The definitions of 'dominance' and 'recessivity' are the classical ones, devised by Mendel. The other three terms suggested here (orthotaxy, metataxy, parataxy) are certainly not urgently needed, and, in fact, will be little used in the discussion which follows. It does seem important, however, to indicate why certain terms already in use by geneticists do not seem fully appropriate for the three symmetric relations, '$\diamond$', '$\leftrightarrow$' and '$\rightleftharpoons$'.

For the relation '$\diamond$' we might consider designations such as 'no dominance', 'intermediate dominance', and 'co-dominance'. In a nomenclature which places no meaning on 'dominance' other than that the heterozygote is regularly indistinguishable from one of the two homozygotes, the statement 'A lacks dominance over B' or 'A is non-dominant to B' would seem to suggest nothing other than a negation of $A \uparrow B$, and, if the system is regular, this leaves not one possibility, but three, namely $A \diamond B$, or $A \leftrightarrow B$, or $A \rightleftharpoons B$.

In many instances of the relation '$\diamond$', the phenotype of the heterozygote may be capable of being regarded as "intermediate" in some sense between the phenotypes of AA and BB. In other cases, it may be possible to say that AB "possesses the properties of both homozygotes," and for such cases the term 'co-dominance' has been recommended (Srb & Owen, 1952). The author suspects that most cases of the relation '$\diamond$' will be found to fit one or the other of these concepts, but it seems possible that cases might occur conforming to neither, or to both. In any event, what is desired is a term which shall be taken to mean only that the three genotypes are phenotypically distinguishable from one another, without saying anything about the nature of the phenotypes which permit this separation, and without implying anything about gene actions or interactions.

The relation '$\leftrightarrow$' immediately suggests a number of genetic phenomena, including heterosis, over-dominance (super-dominance), "hybrid antigens" or other hybrid substances, certain mating-type systems known in plants and animals, and even the pathological syndrome of erythroblastosis fetalis in man and other mammals. Admittedly, some of these require some qualifications with respect to the definition of '$\leftrightarrow$'; nevertheless a general designation for the relation would seem to be desirable. It would hardly seem advised to translate $A \leftrightarrow B$ as 'A is heterotic with B' inasmuch as heterosis is a name given to the general phenomenon of hybrid vigor, which may be not at all or only in part attributable to "single gene over-dominance." The

latter term is used to describe situations in which the heterozygote is "superior to either homozygote" (cf. Crow, 1952). But even if all cases of the relation '↔' could be viewed in quantitative terms, they would not necessarily conform to the idea of over-dominance for two reasons. The latter term does not specify that the two homozygotes must be indistinguishable in grade, as is required by the definition A ↔ B. Moreover, A ↔ B does not imply that the phenotype of AB be "superior" to AA and BB on any quantitative scale.

Hybrid antigens or other hybrid characteristics, insofar as they are conceived as resulting from heterozygosity at a single locus, would conform to the definition of A ↔ B, provided that no other recognized effect of A and B permitted a differentiation of AA and BB. Also conforming to the definition are the "multiple alleles" responsible for the sex difference in diploid individuals of the parasitic wasp, *Habrobracon juglandis* (Whiting, 1940). With two such alleles, *xa* and *xb*, we obtain phenogram 2-2-2; with three *xa*, *xb* and *xc*, we have phenogram 3-2-3 (fig. 6). It is true, of course, that males of this species are normally, or more commonly, haploid. But with respect to diploid members of the species, the genotype-phenotype relations for sex are described by these two systems, when $m = 2$ or 3. Similarly, we could

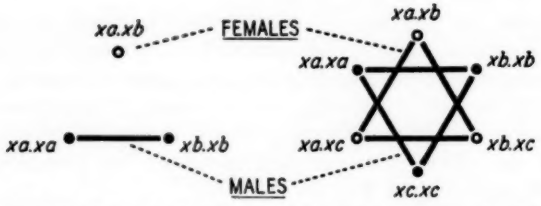


FIG. 6. Phenograms 2-2-2 and 3-2-3, illustrated by multiple allelic sex determination in diploid wasps of the genus Habrobracon.

use the methods of this paper for characterizing any regular phenotype system arising from sex-linked alleles, provided that we were content to describe the phenotype system for the diploid or homogametic sex only.

Hemolytic disease of the newborn, due to maternal-fetal antigenic incompatibility, is a syndrome which can arise only in heterozygotes, since the mother must lack the genetic factor for the sensitizing antigen of the fetus. However, only a small proportion of heterozygous babies develop the disease. Considering any single antigenic system, such as the *K-k* (Kell-Cellano) factors, the phenotype system (hemolytic disease *vs.* normal) might be described as an intermediate state between phenograms 2-2-2 and 2-1-1, i.e. as an ***irregular*** manifestation of the relation '↔'. This, of course, is a very incomplete summarization of the known facts; however, it is at least accurate as far as it goes, and carries with it some definite implications regarding the genetic behavior, e.g. effects of selection, inbreeding, familial appearances (cf. Haldane, 1942; Penrose, 1946). It reminds us, too, that the relation '↔' need not imply an unusual mode of gene action but may come about through an unusual heredity-environment interaction.

Additional examples of the relation '↔' will be mentioned in section 7. Discussion of the relation '⇌' will be postponed until section 6.

6. CLASSIFICATION OF 3-ALLELE PHENOGRAMS BY MEANS OF TWO-ALLELE RELATIONS

We now wish to ask: How satisfactorily will the 5 two-allele relations permit us to describe the 52 three-allele phenograms? A preliminary consideration will show that they could be expected to do so only with considerable ambiguity. We have found that there are 203 three-allele systems possible if one counts the permutational images of all phenograms. Yet, even if it were possible to use the 5 two-gene relations independently in connecting A with B, B with C, and A with C, we could make a total of only 5^3 or 125 statements. Moreover, certain combinations of statements relating A with B and B with C will be found to exclude certain relations between A and C.

A Theorem Concerning Dominance

As a first example, consider the compound statement

$$A \rightarrow B \,.\, B \rightarrow C \,.\, A \rightarrow C$$

specifying three dominance relations between three alleles. For greater compactness, we can arrange the gene symbols in the form of a triangle and, upon replacing the sign '$\supset$' in the definition '$\rightarrow$' by the identity bar of a genotype diagram, we observe that

Six of the 15 relations between pairs of genotypes are not explicitly defined by the statements $A \rightarrow B$, $B \rightarrow C$ and $A \rightarrow C$, and these are shown in the diagram by dotted lines. However, all of these are implicit under the system, being deducible from the transitivity of '$\supset$' as follows:

$$(AB \supset AA \,.\, AA \supset AC) \supset AB \supset AC$$

$$(AB \supset BB \,.\, BB \supset BC) \supset AB \supset BC$$

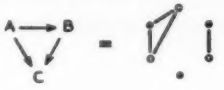
$$(AC \supset AB \,.\, AB \supset BC) \supset AC \supset BC$$

$$(AB \supset AC \,.\, AC \supset CC) \supset AB \supset CC$$

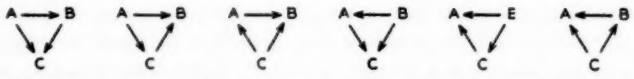
$$(AC \supset AB \,.\, AB \supset BB) \supset AC \supset BB$$

$$(BC \supset AC \,.\, AC \supset AA) \supset BC \supset AA$$

Consequently, the statement $A \rightarrow B \,.\, B \rightarrow C \,.\, A \rightarrow C$ is seen to be free of ambiguity and defines one particular image of phenogram 3-3-6:



Now, three alleles can be connected by dominance ($\uparrow$) relations in 2^3 or 8 ways. Six of these correspond to the 6 permutational images of 3-3-6, already exhibited in figure 4, which may now be represented as:



The remaining two correspond to the two permutational images of 3-3-1:

In either case we see that if the relations between three alleles are capable of being described solely in terms of 'dominance', then the system is thereby *uniquely* described. This property of the relation ' $\uparrow$ ' can be shown to hold generally, and we may state this principle in the following definition and theorem.

DEFINITION 11. *A regular phenotype system of degree m is called a* **dominantly-connected** *system if* $I \uparrow J$ *for all I and J which are different members of the set of alleles* A, B, $\cdots$ M.

THEOREM. *There exist* 2^s *dominantly-connected systems of degree m, where* $s = \frac{1}{2}m(m-1)$, *each of which has index* $\Phi = m$, *and each of which is uniquely defined when all relations* ' $\uparrow$ ' *in* $I \uparrow J$ *are replaced by* '$\rightarrow$' *or* '$\leftarrow$'.

Proof: (a). From definitions 10, 6 and 7, we have $(I \uparrow J) \supset (II \mathfrak{D} JJ)$. Hence, from definition 11, no two homozygotes have identical phenotypes, and so $\Phi \not< m$.

(b). Also, from definitions 10, 6 and 7, $(I \uparrow J) \supset IJ\mathfrak{J}(II \cap JJ)$. Hence, from definition 11, no phenotype is associated with a set of genotypes comprised exclusively of heterozygous genotypes, and so $\Phi \not> m$. Therefore $\Phi = m$.

(c). For any three alleles in the set, say I, J and K, $(I \uparrow J \,.\, J \uparrow K \,.\, I \uparrow K) \supset IJ\mathfrak{D}KK$, because if $IJ\mathfrak{J}KK$, we infer from (b) that $\{IJ\mathfrak{J}KK \,.\, IJ\mathfrak{J}(II \cap JJ)\} \supset KK\mathfrak{J}(II \cap JJ)$, which contradicts (a). Similarly, we must have $IK\mathfrak{D}JJ$ and $JK\mathfrak{D}II$.

(d). For any four alleles, say I, J, K and L, $(I \uparrow J \,.\, I \uparrow K \,.\, I \uparrow L \,.\, J \uparrow K \,.\, J \uparrow L \,.\, K \uparrow L) \supset (IJ\mathfrak{D}KL)$, since if $IJ\mathfrak{J}KL$, we infer from (b) that

$$\{IJ\mathfrak{J}KL \,.\, IJ\mathfrak{J}(II \cap JJ) \,.\, KL\mathfrak{J}(KK \cap LL)\} \supset (II \cap JJ)\mathfrak{J}(KK \cap LL),$$

which contradicts (a). Similarly, we must have $IK\mathfrak{D}JL$ and $IL\mathfrak{D}JK$.

(e). Thus, all $\mathfrak{J}$-relations in a dominantly-connected system are limited to genotype comparisons of the sorts II, IJ and IJ, IK (cf. §4). The former are obviously specified when '$\rightarrow$' or '$\leftarrow$' replaces ' $\uparrow$ ' in $I \uparrow J$, and the latter are also specified for all I, J *and* K, since $(I \rightarrow J \,.\, I \rightarrow K) \supset (IJ\mathfrak{J}II \,.\, II\mathfrak{J}IK) \supset (IJ\mathfrak{J}IK)$, and $(I \rightarrow J \,.\, I \leftarrow K) \supset (IJ\mathfrak{J}II \,.\, II\mathfrak{D}IK) \supset (IJ\mathfrak{D}IK)$, and $(I \leftarrow J \,.\, I \rightarrow K) \supset (IJ\mathfrak{D}II \,.\, II\mathfrak{J}IK) \supset (IJ\mathfrak{D}IK)$, and $(I \leftarrow J \,.\, I \leftarrow K \,.\, J \uparrow K) \supset (IJ\mathfrak{J}JJ \,.\, JJ\mathfrak{D}KK \,.\, KK\mathfrak{J}IK) \supset (IJ\mathfrak{D}JK)$; and similarly for the comparisons IJ, JK *and* IK, JK. Hence any dominantly-connected system is uniquely defined

when all relations '$\uparrow$' in $I \uparrow J$ are specified as $I \rightarrow J$ or $I \leftarrow J$. Moreover, no conceivable network of $s = \frac{1}{2}m(m-1)$ dominance relations is self-contradictory; hence all 2^s dominantly-connected systems are admissible.

The number of dominantly-connected m-allele phenograms is thus simply the number of permutationally distinct ways in which one can connect all pairs of m letters by an arrow ($\uparrow$). Even here, in this simplest case of the general problem of phenograms, the theoretical difficulties presented by such problems of relation "structures" have only recently been resolved by R. L. Davis (1953). His formulae and procedure are too complex to be stated here, but letting d_m stand for the number of dominantly-connected m-allele phenograms, he has shown (in personal communication) that $d_2 = 1$, $d_3 = 2$, $d_4 = 4$, $d_5 = 12$, $d_6 = 56$, and $d_7 = 456$. In general, d_m is much greater than $2^s/m!$.

It is perhaps worth noting that d_m cannot be found merely by listing the "sequences" of numbers specifying how many alleles each gene dominates; such a procedure suffices for $m \leq 4$, but not for $m \geq 5$. For example, the two 5-allele systems, S = (A→B . A←C . A←D . A←E . B→C . B→D . B→E . C→D . C←E . D→E), T = (A→B . A←C . A←D . A←E . B→C . B→D . B←E . C→D . C←E . D→E), are both characterized by the sequence 32221, but they are clearly non-isomorphic, as may be seen from the fact that gene A dominates only one allele (B) in each system, but B in turn is a 3-dominating allele in S and a 2-dominating allele in T. This fact was pointed out by Landau (1951) in a paper dealing with the equivalent problem of an asymmetric and non-transitive "dominance" relation between members of a society, as exemplified by "peck right" in birds.

The Symmetric Relations in Three-Allele Systems

If in any dominantly-connected system of degree m we replace any r of the s '$\uparrow$' relations by '$\rightleftharpoons$', where $0 \leq r \leq s$ and $s = \frac{1}{2}m(m-1)$, the resulting system, if admissible, retains the property of being uniquely defined by the product of the r '$\rightleftharpoons$' relations and $s - r$ '$\uparrow$' relations.

It is therefore not dominance ($\uparrow$) or parataxy ($\rightleftharpoons$) which can be held responsible for any ambiguities that may arise in characterizing any m-allele phenotype system in terms of its two-allele relations. Rather it is the two symmetric relations '$\diamond$' and '$\leftrightarrow$', which, whenever they occur in any system of three or more alleles, almost invariably leave the system incompletely defined by the product of all two-allele relations. It will be noted that these two relations are alike in having the heterozygote distinguishable from its two parent-homozygotes, i.e.

$$(AA \supset AB \,.\, BB \supset AB) \equiv \{(A \diamond B) \wedge (A \leftrightarrow B)\}.$$

As an example, consider the product

$$A \diamond B \,.\, B \diamond C \,.\, A \diamond C$$

which would ordinarily be described by saying that each of the three genes lacks dominance over its two alleles. Now, the 9 intra-pair genotype comparisons are

specified by $\mathfrak{D}$-relations, and therefore a minimum of restrictions is imposed on the filling of the inter-pair relations by $\mathfrak{Z}$. Thus, the six dotted lines in the diagram

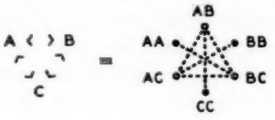
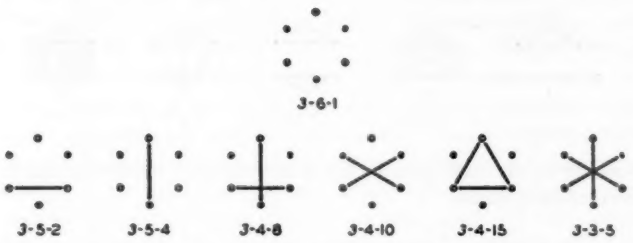


TABLE 3. CLASSIFICATION OF 3-ALLELE PHENOGRAMS BY MEANS OF 2-ALLELE RELATIONS
Encircled numbers refer to degenerate systems

1	A ⟨ ⟩ B, C	6-1, 5-2, 5-4, 4-8, 4-10, 4-15, 3-5	13	A ⟷ B, C	5-3, 4-6, 4-7, 4-9, 3-4, 3-11
2	A ⟨ ⟩ B, C	5-1, 4-3, 4-5, 4-13, 3-10	14	A ⟷ B, C	4-16, 3-17, 2-3
3	A ⟨ ⟩ B, C	4-1, 3-2	15	A ⇌ B, C	4-12, (3-13)
4	A ⟨ ⟩ B, C	4-2, 3-8	16	A ⇌ B, C	3-12
5	A ⟨ ⟩ B, C	4-11, 3-19	17	A ⇌ B, C	3-21
6	A → B, C	3-1	18	A ⇌ B, C	(2-1)
7	A → B, C	3-6	19	A ⇌ B, C	2-7
8	A ⟷ B, C	3-18, 2-4	20	A ⇌ B, C	(2-9)
9	A ⟷ B, C	3-14, 2-2	21	A ⇌ B, C	3-20, (2-6)
10	A ⟷ B, C	3-7, 2-5	22	A ⇌ B, C	2-8
11	A ⟷ B, C	4-4, 3-3, 3-9	23	A ⇌ B, C	(1-1)
12	A ⟷ B, C	4-14, 3-15, 3-16			

can be replaced by identity bars in any combination, so long as $\Im$-relations are not forced into the intra-pair structure and so long as the axiom of transitivity of $\Im$ is not violated. If the six unspecified relations could be filled independently by $\Im$ or $\mathfrak{D}$, there would be 2^6 or 64 systems defined. Actually only 15 combinations are admissible and these correspond to the 15 permutational images of 7 phenograms, as follows:



In all, there are 23 permutationally distinct combinations of the 5 two-allele relations which could be used to describe 3-allele phenotype systems. These relation networks are summarized in table 3. Note that there are only 7 ways in which the 52 systems could be described solely in terms of dominance ($\uparrow$) or lack of dominance ($\diamond$), and all but two of these networks define two or more phenograms; moreover, 32 of the phenograms would be left unaccounted for. Few of the 3-allele systems are uniquely defined by the two-allele relations, the most interesting exceptions being the two dominantly-connected systems, 3-3-1 and 3-3-6. The table demonstrates that each of the 5 two-allele relations is *non-transitive*, i.e. (A R B . B R C) neither implies nor excludes A R C, where R stands for any one of the five relations.

One possible way in which to reduce somewhat the ambiguity introduced by the symmetric relations '$\diamond$' and '$\leftrightarrow$' in multiple allelic systems would be to define certain relations which, in addition to specifying the intra-pair genotype comparisons, also specify, at least in part, the inter-pair comparisons (cf. §4). Four examples will be considered here, these defining certain sub-relations of the relations '$\leftrightarrow$' and '$\rightleftarrows$' which are of special interest.

Degenerate Systems and Iso-allelism

As noted in section 2, the identity system 2-1-1 can well be disregarded in enumerating the regular phenotype systems involving only two alleles. However, the statement A $\rightleftarrows$ B does not imply that the distinction between A and B is indeterminate in systems having three or more alleles. Accordingly, we wish to distinguish two sub-relations of '$\rightleftarrows$' which are mutually exclusive when the field of '$\rightleftarrows$' is restricted to multiple alleles ($m \geq 3$):

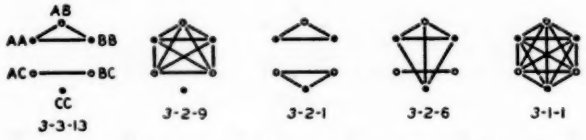
DEFINITION 12. (A $\cong$ B) $\equiv$ (A $\rightleftarrows$ B. A$I\Im$BI), *for all* I, *where* I *stands for any allele of the set* A, B, · · · M *other than* A *or* B; *with* $m \geq 3$.

DEFINITION 13. (A $\simeq$ B) $\equiv$ (A $\rightleftarrows$ B. A$J\mathfrak{D}$BJ), *where* J *stands for at least one allele of the set* A, B, · · · M *other than* A *or* B; *with* $m \geq 3$.

The relation '$\cong$' is termed *equivalence*, and any m-allele system involving at least

one pair of equivalent alleles is described as *degenerate*, since it cannot be recognized except as a system of degree k, where $1 \leq k < m$.

These definitions are easily illustrated for the case $m = 3$. As is shown in table 3, there are 11 three-allele phenograms incorporating the relation A $\rightleftharpoons$ B. Of these, 5 exemplify the relation A $\cong$ B, having AC$\mathfrak{Z}$BC:



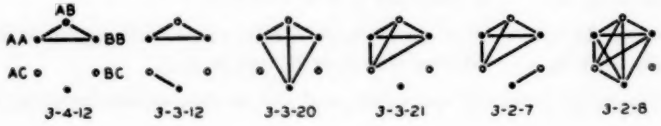
In corresponding order, these systems are observationally indistinguishable from the following two-allele systems:

Thus, the 52 three-allele phenograms include 5 degenerate phenograms, four of which are recognizable only as 2-allele systems, and one of which (3-1-1) represents the completely degenerate or identity system.

It will be noted that phenograms 3-2-1 and 3-2-9 reduce observationally to the same two-allele phenogram, 2-2-1, i.e. two alleles 'with dominance.' We therefore observe an exception to the general rule that different phenograms of the same degree will exhibit different statistical properties or "genetic behavior"; they fail to do so when they are both degenerate and identifiable with different permutational images of a single non-degenerate phenogram of lower degree. The number of exceptional cases of this kind will greatly increase with increasing m, but the proportion of such phenograms among the total n_m always remains very small.

The fact that each of the 5 two-allele systems (counting both images of 2-2-1, as well as 2-1-1) corresponds to a different degenerate phenogram of degree 3 might lead one to suppose that the number of degenerate phenograms of degree m is always N_{m-1}. Such, however, is not the case, as a consideration of the various 3-allele systems and their degenerate 4-allele counterparts will show. Again, a general formula has not been evolved, but for $m \geq 4$ it appears that the number of degenerate m-allele phenograms will always be considerably less than N_{m-1} though obviously not less than n_{m-1}.

There remain for consideration the 6 three-allele phenograms having A $\rightleftharpoons$ B with AC$\mathfrak{D}$BC, illustrating the interesting relation A $\simeq$ B:



Given sufficient genetic data of the proper kinds, each of these systems should be capable of being recognized as a 3-allele system. In practice, however, some of these systems would pose considerable analytical difficulties, particularly in relation to human genetical data. In general, assuming not too unequal phenotype frequencies, phenogram 3-4-12 would be expected to offer least difficulty in the way of recognition. Here the presence of four phenotypes rules out the possibility of a *regular* two-allele system. Moreover, on the assumption of a simple population genotype equilibrium, a test of goodness of fit of the system could be made on a sample of unrelated individuals; since $\Phi = 4$ and $m = 3$, a single degree of freedom remains for the test.

An interesting example of 3-4-12 is afforded by the hypothesis recently set forth by Itano (1953) in explanation of certain facts regarding the inheritance of various forms of human hemoglobin. In essence, his theory postulates three normal "iso-alleles," $Sk^{1.4}$, $Sk^{1.9}$ and Sk^{3}, accounting for different ratios (a/b) of normal (a) and abnormal (b) hemoglobins when these genes occur in heterozygotes for the sickle-cell gene, sk^{b}, while, at the same time, having no known properties which permit a differentiation of the 6 genotypes formed by their *inter se* combinations; hence having the relations: $Sk^{1.4} \simeq Sk^{1.9}$, $Sk^{1.9} \simeq Sk^{3}$, and $Sk^{1.4} \simeq Sk^{3}$. To illustrate system 3-4-12,

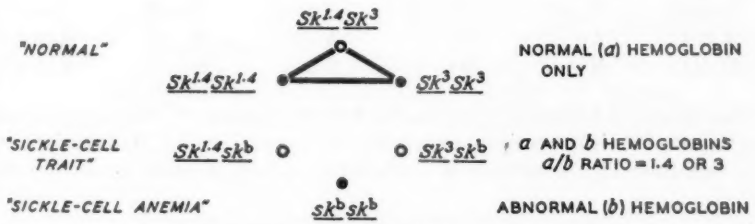


FIG. 7. Phenogram 3-4-12, illustrated by Itano's hypothesis

the present author has chosen to consider the genotype-phenotype relations relative to sk^{b} and two of the "iso-alleles" (fig. 7).

The term 'iso-alleles' was introduced by Stern and Schaeffer (1943) and defined as "alleles indistinguishable except by special tests." A somewhat fuller definition is given by Green (1952): "allelic genes which when homozygous produce phenotypes indistinguishable from one another, but which can be separated from each other by special tests." We note that the latter definition does not exclude the relation '$\leftrightarrow$' since AA$\}$BB implies either A $\leftrightarrow$ B or A $\rightleftharpoons$ B. Curiously, in their study of three wild-type or normal iso-alleles of the *cubitus interruptus* locus in *Drosophila melanogaster*, Stern and Schaeffer make no mention of heterozygotes for any two of the three iso-alleles. Presumably such were produced in the course of the experiments and were found completely normal in wing venation, but there is no mention of this. As noted in section 2, the relation '$\leftrightarrow$' in system 2-2-2 implies a certain kind of "indistinguishability of alleles," but this does not refer to the identification of genotypes by combined phenotypic and test-mating observations (unless, as in the case of sex-determining alleles of Habrobracon, one is restricted to matings between phenotypes).

But, although the intended meaning is not very clear with respect to the relation

'$\leftrightarrow$', the term 'iso-allelism' seems particularly appropriate for the relation '$\simeq$' of this paper, and this is evidently one of the principal usages intended by Stern and Schaeffer and by subsequent writers. When three genotypes, AA, AB and BB, are phenotypically indistinguishable, one "special test" which may reveal the difference between A and B is provided by the comparison AC⫐BC, where C represents a third allele. The term 'iso-allelism' will therefore be used here as a designation for the relation '$\simeq$', although it must be emphasized that a variety of other meanings are also attached to the term.

If R stands for any one of the five 2-gene relations (definitions 5–9) and I stands for any allele other than A or B, it is easily proved from definitions 12 and 13 that $(A \cong B \,.\, A\ R\ I) \supset B\ R\ I$, but $(A \simeq B \,.\, A\ R\ I)$ neither implies nor excludes $B\ R\ I$. Thus, in the 5 three-allele phenograms having $A \cong B$ each system is symmetric with respect to transposition of the two equivalent alleles A and B, whereas in the 6 phenograms having $A \simeq B$, the two 'iso-alleles' may exhibit the same or different relations with respect to C. These six systems are in fact uniquely described by the following products:

3-4-12	3-3-12	3-3-20	3-3-21	3-2-7	3-2-8
$A \simeq B$	$A \simeq B$	$A \simeq B$	$A \simeq B$	$A \simeq B$	$A \simeq B$
$A \diamond C$	$A \leftarrow C$	$A \leftrightarrow C$	$A \rightarrow C$	$A \rightarrow C$	$A \simeq C$
$B \diamond C$	$B \diamond C$	$B \leftrightarrow C$	$B \diamond C$	$B \leftarrow C$	$B \leftrightarrow C$

Phenogram 3-2-8 illustrates one property of the relation '$\simeq$' which might suggest that 'iso-allelism' is not entirely appropriate for the relation '$\simeq$'. As is easily proved from definition 12, the relation of 'equivalence' is both symmetric and transitive, i.e.

$$(A \cong B) \supset (B \cong A)$$

and $$(A \cong B \,.\, B \cong C) \supset (A \cong C), \text{ for } m \geq 3,$$

so that in any system of m alleles it would always be possible to delimit a subset of 'equivalent alleles', if indeed the existence of such were known from classifications made under other circumstances. By contrast, the relation '$\simeq$' is symmetric, but it is *intransitive* in systems of three alleles, as is shown above in phenogram 3-2-8, and non-transitive in systems of 4 or more alleles. More exactly,

$$(A \simeq B) \supset (B \simeq A)$$

but $$(A \simeq B \,.\, B \simeq C) \supset (A \leftrightarrow C) \qquad \text{if } m = 3,$$

and $$(A \simeq B \,.\, B \simeq C) \supset \{(A \simeq C) \wedge (A \leftrightarrow C) \wedge (A \cong C)\} \qquad \text{if } m \geq 4.$$

Thus, if we accept 'iso-allelism' as a designation for '$\simeq$', we may be able to use the terms 'iso-allelic' and 'iso-allelism' without ambiguity, although it may not always be possible to designate a subset of 'iso-alleles' the members of which are all connected by the relation '$\simeq$' as in the example $Sk^{1.4}$, $Sk^{1.9}$ and Sk^{3}.

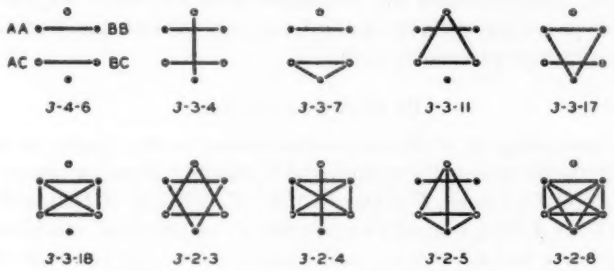
Systems with Symmetric Gene Frequency Solutions

Just as the statement $A \rightleftharpoons B$ does not imply an indeterminacy of the *degree* of the system if $m \geq 3$, the statement $A \leftrightarrow B$ does not imply indeterminacy of the *ratio of the two gene frequencies* $(p:q)$ in ordinary population samples if the system involves three or more alleles. Corresponding to the two relations '$\cong$' and '$\simeq$', we therefore define two sub-relations of the relation '$\leftrightarrow$' as follows:

DEFINITION 14. $(A \doteq B) \equiv (A \leftrightarrow B \,.\, AI \Im BI)$, *for all I, where I stands for any allele of the set* A, B, $\cdots$ M *other than* A *or* B; *with* $m \geq 3$.

DEFINITION 15. $(A \dot{-} B) \equiv (A \leftrightarrow B \,.\, AJ \mathfrak{D} BJ)$, *where J stands for at least one allele of the set* A, B, $\cdots$ M *other than* A *or* B; *with* $m \geq 3$.

There are 24 three-allele phenograms incorporating the relation $A \leftrightarrow B$, and 10 of these illustrate the relation $A \doteq B$, having $AC \Im BC$:



These systems, like those incorporating the relation $A \cong B$, have the two alleles A and B symmetrically disposed in all phenotypes, and $(A \doteq B \,.\, A\,R\,I) \supset B\,R\,I$ for all I, where I is any allele other than A or B. Under a simple Hardy-Weinberg equilibrium, all phenotype frequencies are therefore symmetric functions of p and q, the frequencies of alleles A and B, respectively. A random sample of unrelated individuals drawn from such a population cannot therefore yield unique solutions for p and q in any case. Moreover, unlike the situation in phenogram 2-2-2 (cf. §2), not all systems incorporating the relation '$\doteq$' will yield even an estimate of the frequency of heterozygosis (2θ) for A and B. System 3-2-3, for example, makes possible only an estimate of the frequency of all three heterozygous classes taken together.

The relation '$\dot{-}$' is illustrated by 15 three-allele phenograms: 3-5-3, 3-4-4, 3-4-7, 3-4-9, 3-4-14, 3-4-16, 3-3-3, 3-3-9, 3-3-14, 3-3-15, 3-3-16, 3-3-17, 3-3-20, 3-2-2, and 3-2-6. One of these systems, 3-3-17, is defined by the product $A \doteq B \,.\, B \dot{-} C \,.\, A \dot{-} C$ and is thus also counted among the 10 phenograms exhibiting the relation '$\doteq$'. It is not yet known which of these systems permit a unique solution of the three gene frequencies, p, q and r, under a simple genotype equilibrium. Those phenograms having $\Phi < m$, including therefore 3-2-2 and 3-2-6, will certainly never do so, and the same applies to 3-3-17. But some of these systems will almost certainly yield a unique solution for p, q and r, at least for some phenotype frequency ratios; they

thus escape the kind of indeterminacy characterizing the relation '↔' in phenogram 2-2-2.

7. EXAMPLES FROM HUMAN BLOOD-GROUP SEROLOGY

So far we have merely presented a catalogue of theoretical or conceivable 2- and 3-allele regular phenotype systems and have discussed some classificatory problems pertaining thereto. The question arises: How many of these systems actually occur? If most of them were to be regarded as biologically implausible, or, at any rate, if most of them were nowhere exemplified in genetics, one might be forced to admit that many of the aforementioned terminological difficulties could be more imaginary than real.

A consideration of just two human blood-group systems, Rh and ABO, will show that a large proportion of the 52 three-allele systems can or *do* occur, and that ambiguities do arise in attempting to describe these by means of standard genetic nomenclature. These examples will also suggest some alternative ways in which m-allele phenotype systems could be classified, and they will introduce further problems to be dealt with more extensively later.

Rh Blood-group Systems

Without mentioning all of the complexities known in this system, we may recall that current theory accepts the existence of 8 principal alleles, or classes of alleles: R^1 (CDe), R^2 (cDE), r (cde), R^0 (cDe), r' (Cde), r'' (cdE), R^z (CDE), and r^y (CdE). The letters C, D, E, c, d, e stand for properties of the red blood cells identifiable by means of antisera anti-C, andi-D, anti-E, anti-c, anti-d, anti-e, respectively. The theory specifies that each of these properties will be present if at least one of the four alleles determining it (as indicated by the bracketed symbols) is present in the genotype. We shall assume that all six antisera are available, having potencies sufficient for detecting the properties in accordance with this assumption.[7]

The 8 alleles provide a total of $\frac{1}{2} \times 8 \times 9$ or 36 genotypes, but we are free to consider any three alleles at one time, giving a total of 6 genotypes. We shall consider in our example the three alleles which collectively make up about 95 per cent of the totality in the United States, namely CDe (R^1), cDE (R^2) and cde (r). One can, if he chooses, think of a population possessing these three alleles exclusively.

The six antisera partition the six genotypes as indicated in figure 8. In this diagram the three heterozygous genotypes are unlabelled, but they are assumed to be in their standard positions, e.g. CDe/cDE is between CDe/CDe and cDE/cDE at the top of the figure. Employment of any particular antiserum is indicated by a dotted-line partition passing through the figure; for example, anti-E, represented by one of the diagonal partitions, separates three genotypes which react positively with the serum (CDe/cDE, cDE/cDE, cDE/cde) from the remaining genotypes, which react

[7] The existence of property d and antibody anti-d has been the matter of some dispute, but for the sake of symmetry in figure 8 we assume their existence. Actually, d and anti-d are not needed for the illustration of any of the 13 phenograms shown in figure 9; for example, 3-2-1 could have been illustrated alternatively by anti-C, 3-3-13 could have been illustrated by anti-C and anti-c, 3-4-11 could have been illustrated by anti-c, anti-D and anti-E, etc.

negatively. The presence of such a partition line implies, of course, that we dare not connect any two genotypes by an identity bar which crosses the partition.

We may recall (fig. 3) that there are 9 three-allele phenograms having $\Phi = 2$, which is to say that there are 9 distinct ways in which a serum might effect a dichotomous partition of the six genotypes. Hence, we may use the index-2 phenogram numbers to designate the partitions producing them. Thus, the six Rh reagents can be said to provide three 2-1 partitions (anti-C, anti-d, anti-E) and three 2-9 partitions (anti-c, anti-D, anti-e). Moreover, each antiserum can be identified with one of the 3 permutational images of 3-2-1 or 3-2-9.

If all six sera are employed, we obtain phenogram 3-6-1, i.e. all six genotypes are differentiated. However, using any possible combination of the six reagents, including none at all, there are 2^6 or 64 different test batteries. Twenty of these possibilities are shown in figure 9, illustrating all possible phenograms which can be derived. Using a single serum, we obtain either phenogram 3-2-1 (e.g. anti-d) or 3-2-9 (e.g. anti-D); the four additional cases, being permutational images of these two, are not

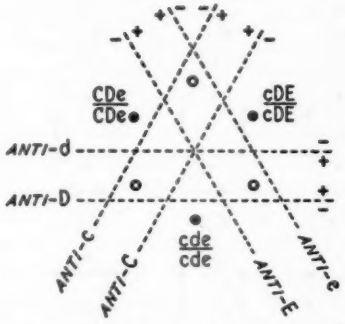


FIG. 8. Partitions of six Rh-genotypes by means of six antisera

illustrated. Using two sera, four phenograms are possible: 3-4-1, resulting from two 2-1 partitions; 3-3-19, resulting from two 2-9 partitions; 3-3-13, resulting from 'parallel' 2-1 and 2-9 partitions; and 3-3-6, resulting from 'non-parallel' 2-1 and 2-9 partitions. Note that these four phenograms possess 3, 3, 3, 6 permutational images, respectively, all of which could be illustrated by the 15 possible pairs of reagents that could be selected.

Altogether, 13 distinct phenotype systems are illustrated by means of the 3-allele Rh example (fig. 9). Four of these are degenerate systems, one being the identity system (3-1-1), and three being recognizable only as 2-allele systems, namely 3-2-1 and 3-2-9 (both of which are observationally equivalent to 2-2-1, i.e. 'dominance') and 3-3-13 (identifiable as 2-3-1, i.e. two alleles with 'no dominance'). It will be noted that three phenograms, 3-6-1, 3-5-2 and 3-4-15, could be described as showing lack of dominance between all three alleles, i.e. $R^1 \diamond R^2$, $R^1 \diamond r$, $R^2 \diamond r$; similarly, phenograms 3-4-11 and 3-3-19 would be identically described in terms of two-allele relations, as would also 3-5-1 and 3-4-3 (cf. table 3, §6). Considering the various antisera

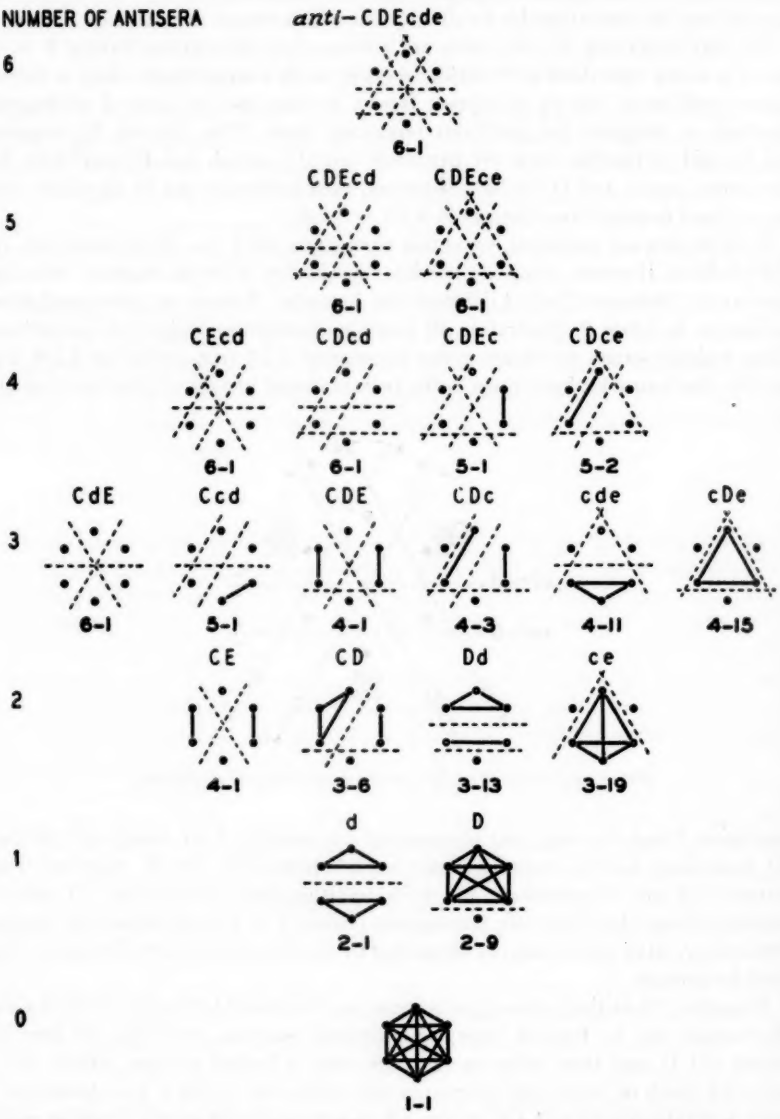


FIG. 9. Thirteen 3-allele phenograms arising from various classifications of 6 Rh-genotypes

in chronological order of discovery (cf. Race & Sanger, 1950), one can trace in figure 9 the following evolution of R^1-R^2-r phenotype systems of increasing index:

	Antisera	*Phenogram*
1938	None	3-1-1
1939–40	Anti-D or anti-C + D	3-2-9 (≡ 2-2-1)
1941	Anti-C, D	3-3-6
1943	Anti-C, D, c	3-4-3
1943	Anti-C, D, c, E	3-5-1
1945	Anti-C, D, c, E, e	3-6-1

It must be emphasized that figure 9 only purports to show the various classificatory possibilities for three arbitrarily selected Rh alleles. Fifty-five other subsets of the eight principal alleles could be examined in the same way; 7 of these would illustrate the same set of 13 three-allele phenograms, while the remainder would exhibit only 10 of these phenograms. To say that all six genotypes in figure 8 are differentiated from one another by means of the six antisera is not to say, of course, that all of these genotypes are thereby uniquely separated from all other known genotypes. Nor could we expect such a diagram to anticipate, so to speak, all of the complexities inherent in an 8-allele system. It will be noted, for example, that the geometry of figure 8 invited—although it did not demand—the representation of anti-C and anti-c by parallel (non-intersecting) partition lines. No 'space' is therefore provided for one or more conceivable genotypes reacting negatively with both anti-C and anti-c; and similarly for anti-D and anti-d and for anti-E and anti-e. But even neglecting the possibility of "double-negative" reactions for these three pairs of reagents (actually, only a few such bloods have been reported), there remain 3^3 or 27 possible combinations of reactions. By contrast, the six intersecting partition lines in figure 8 give rise to only 18 phenotype compartments; hence, the 6 occupied and 12 unoccupied compartments could accomodate some, but not all, of the additional genotypes containing the alleles R^0, r', r'', R^z and r^y.

Immune antisera not infrequently contain two or more antibody "fractions" which can be separated by absorptions, and use of such polyvalent or "compound" reagents offers in general another means of modifying the phenotype system. However, in figure 8 it will be observed that any serum containing two or more antibodies of the six specificities indicated would be expected to either agglutinate the cells of all 6 genotypes under consideration or to duplicate one of 2-9 partitions effected by the "pure" reagents, anti-c, anti-D, or anti-e. For example, a serum containing both anti-C and anti-E in sufficient concentrations (anti-C + E) might be expected to partition the 6 genotypes in the same manner as anti-D, and the same could be said for anti-C + D and anti-C + D + E. Conversely, as is seen in figure 9, when any two 2-1 partitions are employed (e.g. anti-C and anti-E), one of the 2-9 partitions (e.g. anti-D) becomes superfluous; the three 2-1 partitions alone are capable of yielding phenogram 3-6-1.

Diagrams exactly like those of figure 8 and figure 9 would be exemplified by many sets of three alleles in the very complex "B system" of bovine blood groups. If we have three alleles $X^{ABD\cdots}$, $X^{BCE\cdots}$, and $X^{ACF\cdots}$, then the three 2-9 partitions are furnished

by anti-A, anti-B and anti-C, while the three 2-1 partitions are furnished by anti-D, anti-E and anti-F. There are many other possible serological interpretations of a diagram like figure 8, making use of simple assumptions concerning gene actions and diagnostic criteria. For example, assume three alleles, X^A, X^B and X^C; the three 2-1 partitions are given by anti-A, anti-B and anti-C and the three 2-9 partitions by anti-A + B, anti-A + C and anti-B + C. The latter illustration shows that even when we assume only *one observable property per gene*, we can still obtain no less than 13 distinct 3-allele systems through use of diagnostic criteria (e. g. serologic reagents, chemical procedures, color-vision tests) which detect these properties *singly* and *in pairs*. The failure of 'lack of dominance' and other 2-allele relations to uniquely define some of the common 3-allele systems is therefore one which need not be attributable to the assumption of more than one observable property per gene, an assumption used in the Rh example.

In a 3-allele diagram having the standard arrangement of genotypes there are four kinds of 2-partitions which can be simply represented by *straight lines*, namely 2-1, 2-7, 2-8 and 2-9. In their various combinations such partitions can account for 34 of the 52 three-allele phenograms, and the latter are easily recognized in figure 3 by the fact that their diagrams involve no crossing of identity bars belonging to different phenotypes. The 13 phenograms illustrated by the Rh example exhaust the systems which can be "explained" in terms of 2-1 and 2-9 partitions. To illustrate further possibilities arising from 2-7 and 2-8 partitions, we may now turn our attention to the human ABO blood groups.

ABO Blood-group Systems

The four Landsteiner blood-groups, O, A, B and AB, are ordinarily tested by mixing "unknown" cells with "standard" group A (anti-B) and group B (anti-A) sera. A naturally-occurring mixed or polyvalent reagent, however, is furnished by serum of group O individuals, which, in adults at least, will contain both anti-A and anti-B agglutinins in high titers. Such sera can be designated 'anti-A + B'. Also, because of the so-called "reciprocal relation" which exists between antigens and antibodies in the ABO genotype system, the four blood groups can be tested by mixing "unknown" serum with two "standard" cell suspensions derived from group A and group B individuals, respectively. And again, in the cells of group AB individuals we are provided with another compound "reagent," reacting positively with sera of individuals of groups O, A and B, negatively only with AB. Thus, of the eight components provided by cells and sera of the four groups, only O cells and AB sera are useless as reagents.

We therefore have 6 possible reagents, consisting of three kinds of cells (A, B, AB) and three kinds of sera (O, A, B), giving reactions which partition the six principal ABO genotypes as shown in figure 10.

Since anti-A serum gives the same 2-1 partition as is given by group A cells, and similarly for anti-B and B cells, we actually have only 4 distinct partitions. Using these, again, in all possible combinations, numbering 2^4 or 16, the ABO genotypes can be made to yield 8 three-allele phenograms (fig. 11). We are particularly interested here in partition 2-8, provided by the use of AB cells as reagent. Together with the

two 2-1 partitions and the single 2-9 partition (group O serum), we are presented with three systems not met with in the Rh example, *viz.* 3-3-12, 3-3-18, and 3-2-8.

The last of these is especially interesting. To make the illustration seem concrete, imagine that the ABO groups had been discovered not by Karl Landsteiner but by M. M. Green, who, we shall suppose, has observed that by mixing his own red blood cells with the sera of many individuals two "groups" of individuals can be distinguished: those whose sera agglutinate his cells (phenotype *h*) and those whose sera do not (*H*). The latter group, to which Green himself belongs, is found to comprise only about 5 per cent of the population. After considerable difficulties in securing sufficient genetic data (cf. §§2, 6), Dr. Green would be able to deduce that all members of the phenotype *H* were heterozygotes for the same two alleles, but that homozygotes for either of these were of phenotype *h*, and further, that one or more additional alleles were involved, giving a system such as 3-2-8. On the basis of this, he might then be led to revise his symbols, designating his own group (and genotype) as AB, which, of course, is what he is.

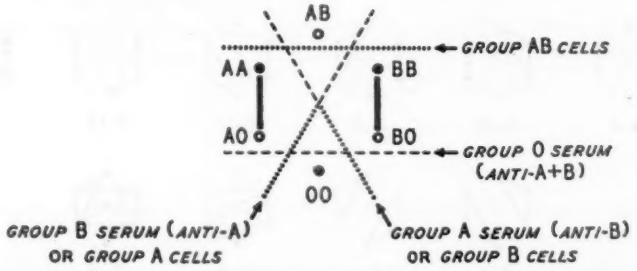


FIG. 10. Partitions of six ABO genotypes by means of three natural serum reagents and three cell suspensions.

In phenogram 3-2-8, resulting from the use of AB cells as the sole reagent, we have a system illustrating both the relation of metataxy (A $\leftrightarrow$ B) and of isoallelism (A $\simeq$ O, B $\simeq$ O). Further systems having A $\leftrightarrow$ B are shown in figure 11, namely 3-3-18, 3-4-6 and 3-3-7, the last two being possible if one assumes the availability of a so-called true anti-O serum.

When tests are performed in the usual way, using anti-A and anti-B sera, we obtain phenogram 3-4-1, and no more complete discrimination of the 6 major genotypes is ordinarily possible. It is customary to describe this system by saying (Srb & Owen, 1952): "L^A and L^B appear as dominant to their allele $l \cdots L^A$ and L^B, however, mutually lack dominance with respect to each other, since the heterozygote L^AL^B is easily identifiable as blood group AB." As we have seen (§6, table 3), this summarization is ambiguous. The statement $L^A \diamond L^B \,.\, L^A \rightarrow l \,.\, L^B \rightarrow l$ implies either phenogram 3-4-1 or 3-3-2; to complete the summary, we should have to add that ll is *not* identifiable with blood group AB, i.e. $ll \supset L^AL^B$. (The gene symbols L^A, L^B, l correspond to A, B, and O, respectively, of figure 10).

Phenogram 3-3-2 could, in fact, be illustrated for the ABO genotype system by assuming an unusual, though *a priori* not irrational, technique of blood typing.

Instead of testing "unknown" cells with standard sera of two kinds, we could use as 'reagent' a mixture of cells and serum of a known group B person. Adding to this an equal volume of a similar 'whole blood mixture' having a cell-serum ratio equal to that of the reagent, we would expect to find: (1) no agglutination (genotypes BB

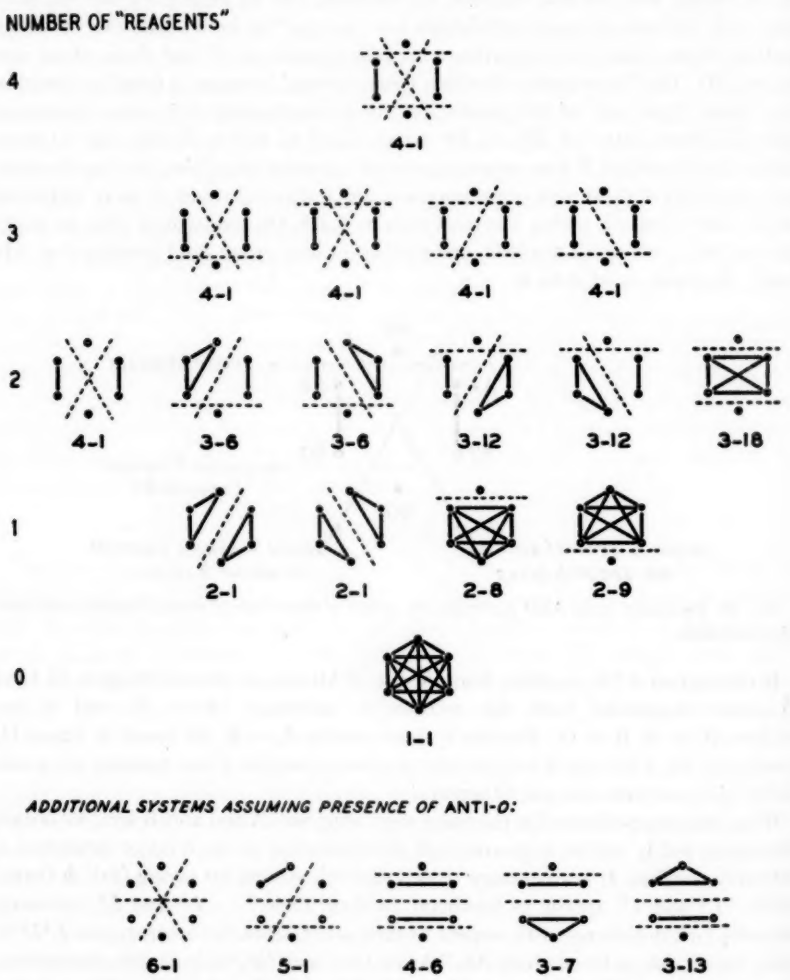


FIG. 11. Thirteen 3-allele phenograms illustrated by the ABO blood group genes

or BO); (2) cells half of which are agglutinated (genotypes AB or OO), or (3) cells all of which are agglutinated (genotypes AA or AO). The resulting phenotype system, 3-3-2, arises from a kind of confounding of two separate reactions, in such a way as to give rise to two 2-7 partitions (fig. 12). In fact, if the reactions were recorded merely

as 'negative' or 'positive', the result would be phenogram 3-2-7, illustrating the relation of iso-allelism (cf. §6).

Another device capable of altering the phenotype system and occasionally used in serology is one which might be called the method of *partial partitioning*. If a collection of bloods is first tested with anti-A serum, subsequent testing with anti-B may be deliberately confined to the A-negative bloods or to the A-positive bloods. In the first case we obtain phenogram 3-3-6, with $A \rightarrow B \,.\, B \rightarrow O \,.\, A \rightarrow O$; in the second case we obtain phenogram 3-3-12, illustrating the relation of iso-allelism, i.e. $A \leftrightarrow B \,.\, B \simeq O \,.\, A \rightarrow O$. The latter case is diagrammed in figure 13, together with two other phenograms not previously illustrated by Rh or ABO examples but made

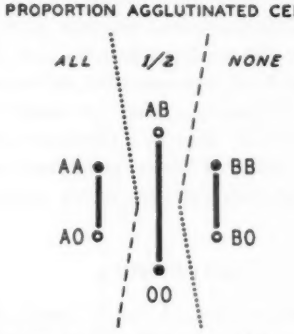


FIG. 12. Phenogram 3-3-2 arising from 'whole blood mixtures' of human bloods

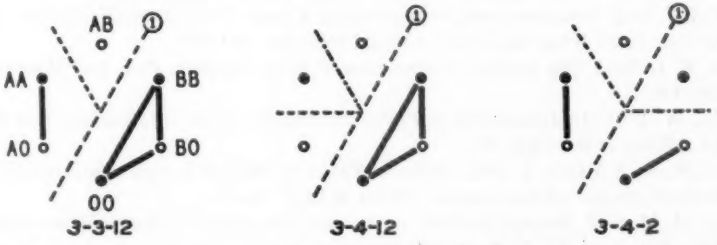


FIG. 13. Three phenograms resulting from combinations of partial 2-1 partitions with a primary 2-1 partition, the latter indicated by ①.

possible through the use of partial 2-1 partitions. Testing schedules of this kind are sometimes employed as a means of conserving one or more precious reagents while searching for bloods belonging to one or more relatively rare phenotypes; for example, anti-B would be conserved in the search for AB bloods in the example shown in figure 13. If the serologic classifications are to be used for genetic analysis, especially gene frequency estimation, the method of partial partitioning will probably be generally avoided, although in some cases it might prove very economical in respect to rare test reagents while entailing little extra work and sacrificing little information concerning gene frequencies. Statisticians will note here some analogies with the device of partial confounding in the design of factorial experiments.

To make one further point, we may briefly consider the A_1A_2BO genotype system. The distinction between the two subclasses, A_1 and A_2, of the A-gene is made possible by means of absorbed group B (anti-A_1) serum. Suppose that a collection of bloods were to be tested with anti-A_1 and anti-B as the sole reagents. The resulting *phenotype system* would again be 3-4-1, but the *genotype system* now involves A_1, B and $(A_2 \cap O)$ instead of A, B and O; the alleles A_2 and O are now confounded, or, in the terminology of this paper, equivalent. Since anti-A serum almost invariably serves as the source of anti-A_1 and is widely available as a naturally-occurring reagent, use of anti-A_1 without anti-A could hardly be expected to arise, except perhaps by accident. No need for a gene symbol to represent $(A_2 \cap O)$ has therefore arisen. In cattle blood-grouping, however, "subtyping" reagents are sometimes available in the absence of the "more broadly reactive" or polyvalent reagents, with the result that intricate variations may arise in both the genotype systems and the attending phenotype systems. Such considerations have recommended the consistent use of the term 'phenotype system' in place of 'genetic system' or simply 'system'. Terms such as "the Rh system" or "the B system" identify a particular genetic locus, but actually specify no particular system, either of alleles (genotypes) or of phenotypes. In this paper we have been concerned with variation in the phenotype system relative to any given genotype system.

REFERENCES

BOYE, C. L. 1941. An allelic series in *Coleus*. *J. Genet.*, Cambr. 42: 191–196

COTTERMAN, C. W. 1951. A note on the detection of interchanged children. *Am. J. Human Genet.* 3: 362–375.

CROW, J. F. 1952. Dominance and overdominance. Chapter 18 in *Heterosis*, edited by J. W. Gowen. Ames, Iowa: Iowa State College Press, Pp. 282–297.

DAVIS, R. L. 1953. The number of structures of finite relations. *Proc. Am. Math. Soc.* 4: 486–495.

FELLER, W. 1950. *An Introduction to Probability Theory and Its Applications*. New York: John Wiley & Sons. Pp. 419.

FISHER, R. A., & YATES, F. 1943. *Statistical Tables for Biological, Agricultural and Medical Research*. Second edition. London: Oliver & Boyd. Pp. 98.

GREEN, M. M. 1952. Mutant isoalleles at the vermilion locus in *Drosophila melanogaster*. *Proc. Nat. Acad. Sc.*, U. S. 38: 300–305.

HALDANE, J. B. S. 1942. Selection against heterozygosis in man. *Ann. Eugen.*, Cambr. 11: 333–340.

ITANO, H. A. 1953. Qualitative and quantitative control of adult hemoglobin synthesis—a multiple allele hypothesis. *Am. J. Human Genet.* 5: 34–45.

LANDAU, H. G. 1951. On dominance relations and the structure of animal societies. I. Effect of inherent characteriatics. *Bull. Math. Biophys.* 13: 1–19.

LEDERMANN, W. 1949. *Introduction to the Theory of Finite Groups*. New York: Interscience Publishers. Pp. 152.

PENROSE, L. S. 1946. On the familial appearances of maternal and foetal incompatibility. *Ann. Eugen.*, Cambr. 13: 141–145.

RACE, R. R., & SANGER, R. 1950. *Blood Groups in Man*. London: Blackwell Scientific Publications. Pp. 250.

SRB, A. M., & OWEN, R. D. 1952. *General Genetics*. San Francisco: Freeman & Co. Pp. 561.

STERN, C., & SCHAEFFER, E. W. 1943. On wild-type iso-alleles in *Drosophila melanogaster*. *Proc. Nat. Acad. Sc.*, U. S. 29: 361–367.

WHITING, P. W. 1940. Multiple alleles in sex determination of Habrobracon. *J. Morph.* 66: 323–355.

WOODGER, J. H. 1937. *The Axiomatic Method in Biology*. Cambridge Univ. Press. Pp. 174.

Contributions of Heredity and Environment to Manifestations of Psycho-Neurosis

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INTRODUCTION

THE PURPOSE of this paper is to review critically recent evidence on the relations between heredity and environment in producing psycho-neuroses. A pedigree will then be given of psycho-neuroses in an Anglo-American Jewish family. This will indicate not only the mode of inheritance but also suspected causes leading to the manifestation of various types of neurotic condition in affected individuals. All previous work has been based on population sampling, no individual family pedigrees having been studied intensely.

Psycho-neuroses include hysteria, neurasthenia, psychasthenia and mental disorders stopping short of insanity; Gates (1946) pointed out the difficulty in assessing the hereditary influence in their manifestation and many psychologists ignore the hereditary aspects. Gates considered it impossible to determine the nature or extent of the hereditary influence. Freud (1933) believed neuroses are serious, constitutionally determined affections seldom restricted to a few outbreaks, but making themselves felt for long periods or even throughout an individual's lifetime. Although neuroses could be greatly controlled by knowing the causes which started them, Freud realized interest in this aspect had lead to neglect of the hereditary or "constitutional factor."

The Brock Report, according to Petrie (1941), stated that inheritance is the commonest single cause of mental disorder; it also emphasized the influence of environmental factors. More recently, Snyder (1947) pointed out that cooperative studies are providing evidence that both heredity and environment modify mental traits: investigators would have to determine objectively when it may be advisable to control either or both. That character expression is altered by variations in environment should not be used as argument against genetic factors helping to develop the trait.

HISTORICAL

Darwin (1873) clearly described psychosomatic effects of emotions such as terror and fear. Actions like trembling and sweating "under certain states of mind, in order to gratify or relieve certain sensations, desires, etc., are still performed under analogous circumstances through mere habit although of no

Received January 10, 1953.

service."[1] Trembling was not useful, often a disservice. It could not originally have been acquired through the will and then made habitual in association with any emotions. Darwin also believed organ neuroses possible, i.e., concentration on a particular organ's behaviour would effect it.

Psychasthenia is a functional neurosis with pathological fear, and anxiety with obsessions, fixed ideas, tics, unreality and self-accusation (Gates, 1946). Diem (1905) found 15% of relatives with general nervous disorders in 1193 cases, while Paskind (1933) found 83% among those of psychasthenias. Comparison of inheritance in psychasthenic nervous disorders, manic-depressive psychosis and schizophrenia showed that psychoses occurred mainly in collaterals, while psychasthenia predominated in the direct line and in sibs. This strongly suggested that psychasthenia was inherited mostly as a dominant.

Gebbing (1932) found neurotic families showed 55% relatives with neuroses, psychoses, psychopathy, debility and organic nervous diseases. The general population had 34%. High frequency of psychiatric and neurological conditions occurred in four families. There was no relation between neuroses and vegetative lability, and few heart or stomach neurotics. Neurotic mode of reaction was an inherited disposition of the nervous system. Lewis (quoted by Gates, 1946) found 37% parents obsessional; in parents of obsessionals also 8% were manic-depressives. There was less connection between anxiety and depression. The same type of psycho-neurosis tended to reappear in a family. Incidence in mothers and fathers was the same.

Paskind (1933) found that 76% of 890 psychasthenic patients showed familial neuropathic tendency. Conditions in relatives included: nervousness, migraine, psychasthenia, hysteria, functional psychosis, epilepsy, senile psychosis, suicide, alcoholism, fainting spells, apoplexy, writer's cramp, defective mental development and psychopathic personality. In 71% a tendency was found in parents who also showed nervous disorders in 51%, contrasting strongly with psychasthenia in relatives of normals.

Newman (1933), studying normal twins, showed genetical influences produced emotional variations. McInnes (1937) supported the view that neurotics are more heavily "loaded" than the average and suggested anxiety neurosis might result from a specific hereditary factor, or group of factors, operating in some individuals to produce emotional disorders. He found 8% with parents having neurotic anxiety in 75 controls, 28% of 50 anxiety cases had one parent showing anxiety neurosis and ten of thirty hysterics had a parent with some psychic abnormality, such as hysteria, epilepsy or asthma. Jealousy never produced anxiety neurosis, even though it caused hysteric breakdown. Important differences possibly existed between family histories of anxiety neurotics, hys-

[1] Darwin suffered from an anxiety neurosis most of his life: he is perhaps here describing his own symptoms.

terics and normals. Certain situations often related to sex life could, amongst others, cause anxiety neurosis. This tended to run truer to type than hysteria; neurotic trends occurred more often in children with neurotic or psychotic parents. McInnes preferred not to draw conclusions on possible inheritance in anxiety states and hysteria, owing to the difficulty in assessing how much was congenital, e.g., dependent on intrauterine toxic factors or anomalies of libidinal development in infancy. To attempt a balanced perspective, he drew attention to the constitutional factor without minimising the great importance of the psychogenic factor. Many neuroses arose from psychic conflict in patients seemingly without constitutional predisposition. This conflict was generally intense and activated by powerful outside causes; recovery followed psychotherapy. At the other extreme were patients with consistent tendency to break down under ordinary or even trifling strains. Here one could postulate a constitutional neurotic tendency. All grades of combinations of factors occurred between these extremes.

Brown (1942) classified neuroses as anxiety states, hysteria and obsessionals; one can get a combination in a single individual. He found in 104 cases that 47% of the parents of anxiety states were normal, compared with 81% normals in the control; 21% of parents also suffered from anxiety states. For hysteria 41% parents were normal and 19% hysterics, while in obsessional states 50% parents were normal and 7.5% obsessional. Psycho-neuroses were inefficient and escapist reactions of qualities inherent in human nature and biologically useful unless exaggerated. Their heredity was difficult to study as children might imitate their nervous parents. Evidence from four pairs of fraternal twins, only one of each pair being psycho-neurotic, but closely resembling one another physically, strongly suggested not only genetical control but also lack of connection with physical traits. Brown concluded that inheritance was neither recessive nor simple dominant, although the latter might be true for some families. Such conclusions were based on mass data, not on actual pedigrees.

Ross (1943), studying the connection between psycho-neuroses and psychoses, found in over a thousand neurotics less than five per cent in 3–10 years became insane and less than one per cent likely to commit suicide. He emphasised that there was not one but several causes favouring the growth and development of nervous illness. Neurotics were thus not especially liable to psychoses. This suggests that the same genes are not involved in manifestations of these diseases, or they are not linked if different genes are involved.

Slater and Slater (1944) in a survey of two hundred neurotic soldiers found family history, previous life and personality more important than war stresses in neurotic breakdown. There was a familial incidence of neuroses and psychopathy. Three classes recognised were: hysteric, anxiety and depressive; relatives of each of these have excess of the others. Two hundred war patients had the

same mean age and mental activity as normals. They concluded that the genetic determinants producing a neurotic constitution are generally non-specific and additive in effect, each producing reduced resistance to stress. Their hypothesis was that many small genes produce additively reduced resistance to some environmental stresses; extremes of the normal range of variation thus have greater susceptibility.

Hyde and Chisholm (1944) compared mental disorders of different races in Boston, Mass. They found Chinese free from alcoholism and with little psychopathy, while Irish, negroes and Italians rated highest. Negroes, Chinese, Russians, Jews and Portuguese were in descending order for psycho-neurosis. Jews also showed low mental deficiency and psychopathy combined with high psycho-neurosis.

Slater (1943–45) after studying 2,000 neurotic soldiers, concluded that different neurotic groups fade into one another clinically. There are no qualitatively distinct groups. Positive family history, childhood neurosis, poor work record, previous nervous breakdown and abnormal personality are all inter-related. Electro-encephalography showed 25% abnormalities in a general neurotic group compared with 10% in the ordinary population. Neurotic constitution is according to Slater and Slater (1944) predominantly determined by very many genes with small effects, i.e., inheritance is polygenic. These polygenes produce reduced resistance to some environmental stresses, thus facilitating a neurosis. The neurotic thus represents one extreme of normal human variation.

Miller (1947) noted increasing recognition of emotional factors causing obscure physical symptoms, e.g., feeling ill during stress. Some conditions, such as neurotic headache, have a family history. Neurotic symptomology often ran in families by imitation, but sometimes perhaps because of a "common structural substrate."

Penrose (1949) pointed out that the genetics of psycho-neuroses has not been studied much, partly because the facts are elusive and partly because environment produces marked changes in psychological reactions. He considered there was some degree of familial concentration of neurotic traits, but its significance was not necessarily genetical. There was no indication of any pleiotropic genetical association between neurosis and intellectual defect. On the other hand, Eysenck and Prell (1951) after numerous tests on MZ and DZ twins concluded that the neurotic predisposition is largely hereditarily determined.

CASE REPORTS

There is therefore sufficient evidence as to the genetical background of psycho-neuroses. Yet all previous observations have depended on mass data rather than on intensive analysis of a single family pedigree: such a pedigree is now given (Fig. 1).

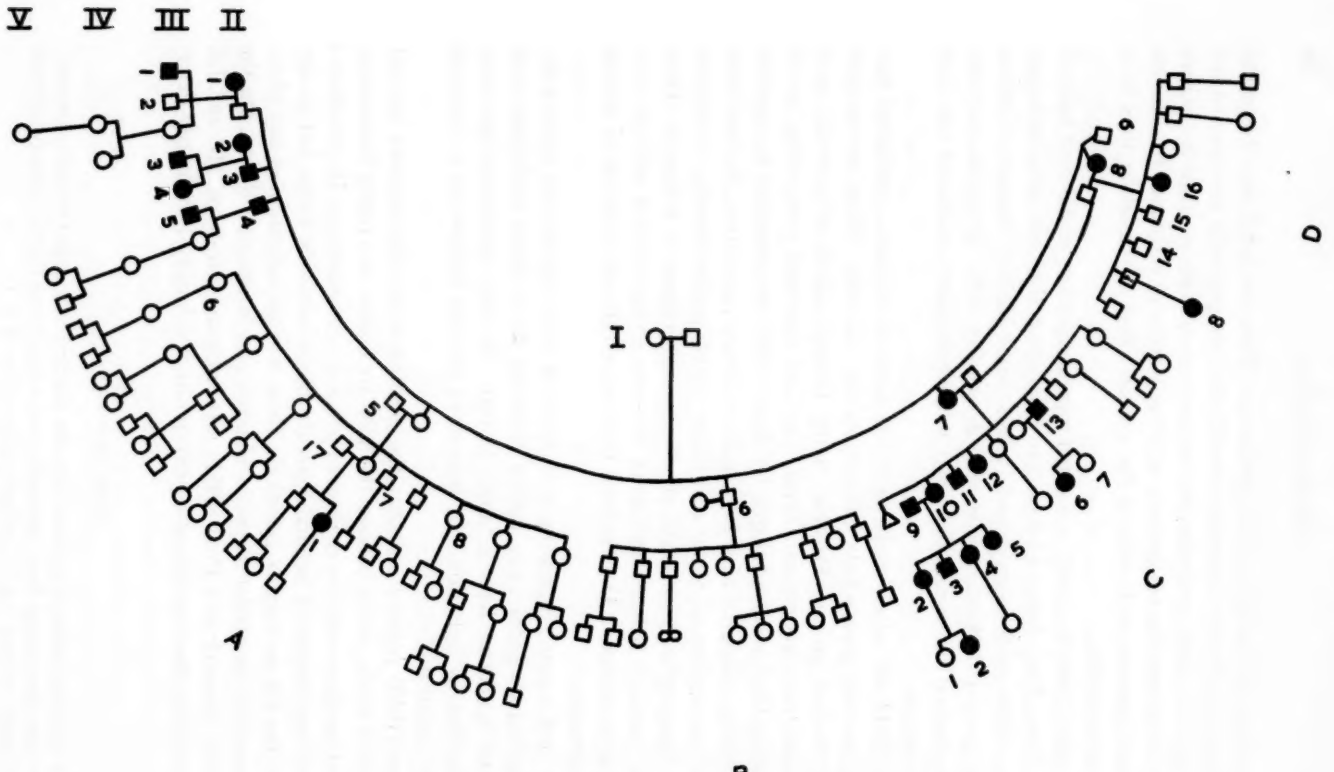

FIG. 1. Pedigree of psycho-neurosis in an Anglo-American Jewish family
A–D are the family groups which have kept together.
Key: ■: Affected males. □: Normal males.
●: Affected females. ○: Normal females.

The investigator has had to judge family tradition for some of the earlier records. This applies to generation I and all but two probands of generation II. With very few exceptions all individuals in generations III, IV and V have been seen either in England or in the United States. Notes are only given for neurotics and others of related interest. Those not recorded are to be assumed normal in the everyday sense of this word.

Generation I. Nothing known of this generation except that tradition says both were normal.

Generation II.

(1) Female. Indistinct, rapid, repetitive speech. Married late.

(2) Female. Shy, nervous, retiring individual. Later developed asthma. Became a recluse, due to excitement of visitors bringing on asthmatic attacks. Lived to *c.* 70 years.

(3) Male. Shy, nervous type.

(4) Male. At c. 36 years lost use of both legs. Family ascribe this to falling off chair; received various hospital treatments. Eventually returned home as incurable. Led active life in wheelchair, working as watch repairer. Intelligent and cultured. Always had full control over bladder; in later years legs withered and had bedsores; ? hysterical paralysis or peroneal paralysis. Died at c. 72 years.

(5) Female. Normal. Married her third cousin.

(6) Male. Normal.

(7) Female. Nervous frightened type. Would easily faint in hot crowded atmosphere or suddenly have to leave table at meals. Frightened of domineering husband. Died from stroke at 53 years.

(8) Female. Nervous type. Frightened of going under railway bridges in case bridge collapsed on her with a train on top. Otherwise able to travel. Went blind in old age.

(9) Male. Twin to preceding. Weakling from birth and died at c.4 years.

Note that II (7) and II (8) married two brothers. Data thus interesting because of double first cousin marriages.

Generation III.

(1) Male. Stutterer. Unmarried. Highly self-conscious, and early gave up travelling job. Following death of father became religious fanatic, making daily visits to synagogue. Took up work of Jewish ritual animal slaughterer.

(2) Male. Normal, but has not married.

(3) Male. Low mentality: considered by family as mentally deficient. Led retiring life; unmarried. Jewish ritual slaughterer. Died suddenly at c. 50 years.

(4) Female. Nervous, retiring type.

(5) Male. Nervous, lazy recluse. Unable to hold jobs (never found work to suit!). Unmarried.

(6) Female. Delicate. Died shortly after marriage from tuberculosis.

(7) Male. Normal. Died in his thirties from Bright's disease.

(8) Female. Normal. Died from arthritis at thirty.

(9) Male. Psychosomatic type. Duodenal ulcer before twenty. Operated upon and recovered. Stomach pains and general upset to vegetative system when anxious, especially over business matters. Highly excitable; occasional periods of grandeur. Has a married brother considered eccentric and reclusive.

(10) Female. Known to have had rare hysterical outbursts with black-outs if thwarted. Neurotic personality (perpetually nagging) but not psychosomatic. For many years upset and obsessed by father's re-marriage to converted Jewess. Married, with four children.

Key: ■: Affected males. ●: Affected females. □: Normal males. ○: Normal females.

(11) Male. Neurotic with psychosomatic symptoms. Nervous breakdown before thirty after service in Great War. Hospitalized after shaking attacks in street, being found in dazed frightened condition. Constantly obsessed by war service for c. 15 years, and by politics. Unmarried and avoids women. Miserly, and quarrelsome habits. Developed "stomach trouble" and diagnosed eventually as neurotic. Recommended to have change of outlook. Moved from London to New York, and now better in health.

(12) Female. Hysterical type with neurotic personality: continually constipated. Married late. No children; prefers dogs to children.

(13) Male. Nervous, quiet individual. Nervous breakdown and hospitalized before thirty during service in Great War. Recovered with no relapse. Married, with two children.

(14) Male. Normal. Unmarried at 50.

(15) Male. Nervous, retiring individual. Unmarried. In late forties.

(16) Female. Neurotic personality; frightened and nervous. Known to have hysterical fits with partial black-outs, e.g., on seeing pictures of snakes, or on seeing tortoises. Married late; no children.

(17) Male. Normal, but religious fanatic. One of four sisters in mental hospital for three years and only brother committed suicide.

Generation IV.

(1) Female. Nervous breakdown lasting several months in late teens following loss of boy-friend. Recovered. Now married and normal, with two children.

(2) Female. "War-baby". Very hysterical as a child: removed from school for short period because "highly-strung". Highly temperamental during adolescence. Married with two children but marital relations unsatisfactory. Had periods of (? neurotic) illness, e.g., nausea, frequencies, backache. Voluntary psychiatric treatment recommended; improvement with psychotherapy and improved relations with husband.

(3) Propositus. Male. Neurotic personality. Poliomyelitis at 21 years (severe attack, unconscious) followed by occasional shuddering attacks. Melanoma of iris (removed) at 26 years; followed by psychosomatic breakdown: collapses, micturition frequencies, diarrhoea, frequently dazed with tenseness leading to death obsession and black-outs, "ulcer" and complete physical collapse. Hospitalized and diagnosed psychosomatic. Phobias (claustrophobia and travelling fears). Underwent psychological treatment; cause attributed to shock in association with continual conflict with family over religious matters, especially relating to inter-marriage. Removed from family. Slow but steady recovery. Now married to Christian wife.

(4) Female. Neurotic. Usually normal but fright of childbirth at 25 years leading, during pregnancy, to inability to walk, morning nausea and gradual collapse into coma. Hospitalized: intra-venous glucose feeding and assurance of personal safety. Recovery after childbirth and now relatively normal, although marital relationship unsatisfactory.

(5) Female. Physically normal but skin affection of nervous origin, arising during periods of stress. (Warned not to worry about it when it occurs). An actress with tendency to faint and neurotic physical symptoms before performances.

(6) Female. Neurotic. Normal till c. 17 years when "stomach trouble", anaemia, giddiness and fright commenced. Incapacitated for work. Continual deterioration for several years with black-outs, travelling phobias and dependence on pheno-barbitone. Believed herself to suffer from several diseases: various treatments (e.g., for heart condition and anaemia). Eventually recommended for psychological treatment. Condition due to conflict with father, and to lesser extent with mother and

maternal grandparents over going out with Christian boy-friends, and wanting to make a mixed marriage. Moved with family from England to New York among Jewish Society and shows improvement.

(7) Female. Normal. 20 years old. Had a Christian boy-friend.

(8) Female. Since mother died from cancer several years ago, became obsessed with dieing from this disease. Father has (? neurotic) "heart condition", causing some incapacitation.

Generation V.

(1) Female. Normal. Aged 12 years.

(2) Female. Neurotic. Normal until aged 8 years. Suffered loss of appetite, stomach pains, general lassitude and general feelings of unwellness. Hospitalized. Diagnosed psychosomatic, attributed to emotional upset resulting from parents' perpetual quarrelling and fear of loss of parental love. Recommended that child be brought up with minimum of parental discord. Recovered, but "tummy-ache" and prostration from excitement prior to parties, etc.

DISCUSSION

One has to be guarded against attributing particular qualities to any human race apart from blood-group frequencies, yet Jewish people are described as highly emotional, and extreme emotions are of a neurotic nature. It has been suggested that Jews may show tendencies different from the population among whom they live, e.g., that tuberculosis rate is somewhat lower, and that amaurotic idiocy is confined to Jewish populations. Familial traits, like those of nervous origin, are often recognised as running within a Jewish family, partly because often its members live close together, and so themselves can observe them. As there is likelihood of more inbreeding amongst Jews than in the general population, owing to social restrictions which religion and custom impose, this helps to bring out characters determined by recessive genes. Dominant characters are more readily seen to be passed on from parents to children, as Jewish families retain their familial ties.

Inheritance for predisposition to psycho-neurosis, regardless of how it is manifested, clearly follows an autosomal dominant mode in the family described above. For example, two sisters (IV (6) and IV (7)) both have the same problems, but whereas one is badly affected, the other is completely free from neurosis. Parents who themselves show neurotic symptoms usually have some neurotic children, while those known to be free do not. In the occasional exceptions there is strong evidence that the neurotic tendency is brought in from parents outside the family who themselves possess neurotic traits. This could happen fairly easily as Jewish immigrants to England at the end of the nineteenth century themselves tended to intermarry with those that had emigrated from similar European countries. Thus genes would be floating in a restricted population. Close inter-marriage is seen in the present pedigree where there is inter-marriage between cousins, and between two brothers with two sisters.

The pattern of inheritance shows similarity to that for early cataract (Stern, 1949), controlled by a dominant gene. This determines occurrence of the disease without specifying the particular type of opacity, attributable to modifiers. Similarly, the symptoms in epiloia are variable, and Gunther and Penrose (1935) attributed this to a dominant gene known only in the heterozygous condition with modifying factors. In the neurotic pedigree it is unlikely that the homozygous dominant is lethal, for there is the instance of two neurotics marrying and having four neurotic children; some of these could possibly be homozygous and show the condition in extreme. Kallmann (1950) attributed schizophrenia to a recessive gene and manic-depressive psychosis to an irregular dominant. Although the latter condition and the neurosis considered here are controlled by dominant genes, it is clear that they are separate entities. Contact with reality is never lost among the neurotics. This means, however, that in some pedigrees there is a possibility that manic-depressive and neurotic symptoms can appear together in the same individual.

There is a tradition in this family that the nervous trouble has come down from the maternal family of Generation II, who originally came from Austria.

TABLE 1. RELATION OF SEX TO NEUROSIS IN A FAMILY GROUP AND PENETRANCE MEASURED BY NUMBER REQUIRING HOSPITALIZATION.

	MALE		FEMALE	
	Affected	Normal	Affected	Normal
Family Group C	3	3	8	9
Number in hospital	3	—	2	—

Therefore only individuals II (7), (8) and (5) could have introduced it into the pedigree. However, only two of these were themselves known to have passed on the nervous condition, which expresses itself in various types of neurotic personality. II (5), who was not known to be neurotic, has given descendants free from the affliction. There is one exception (IV (1)) which can be explained simply: the father has brought in genes for neurosis from another family. This in itself supports the evidence for dominance.

There is no doubt that the pedigree presented suggests that males and females are equally likely to be neurotic. Table 1 gives the number of affected in direct descent in family group C, where many occur. But twice as many affected males have received hospital treatment, suggesting that neurotic symptoms manifest themselves more severely in males.

The causes that have given rise to nervous breakdown in this pedigree are easily recognised and fall into most of the categories recognised by McInnes (1937). Thus loss of sexual partner, fright during war service or fear of pregnancy, emotional insecurity as a result of quarrelling parents, fright following serious illness such as cancer, and conflict over religious and sexual matters. Examples

from the pedigree are listed in Table 2. The neurotic personality thus resolves itself into certain manifestating types, as shown in Table 3. The non-sexual causes may, however, be masking a sexual cause or several causes, acting either concurrently (e.g., IV (3)) or consecutively (e.g., IV (4)). Alcoholism, a neurotic symptom of insecurity or anxiety, is missing from the pedigree, nor are there any excessive smokers. The causes given above have already been included in a list provided by McInnes (1937). They fall roughly into sexual and non-sexual groups. In all cases of young people a cause can be assigned to

TABLE 2. EXAMPLES OF APPARENT CAUSES OF ANXIETY NEUROSIS IN PRESENT PEDIGREE

SEXUAL	PEDIGREE NO.	NON-SEXUAL	PEDIGREE NO.
Marital Incompatibility	III (10)	War Service	III (11)
	IV (2)		III (12)
Unsatisfactory Intercourse	IV (4)	Domestic Strife	V (1)
Conflict over Sex Attachment	IV (3)	Business Worry	III (9)
	IV (6)	Fear of Cancer	IV (3)
Separation from Sexual Object	IV (1)		IV (8)
Fear of Pregnancy and Childbirth	IV (4)		
No Attributable Cause	II (8)		

No examples of coitus interruptus, worry over illegitimacy, influenza, oral sepsis or failure of vision were found in the pedigree.

TABLE 3. MANIFESTATION OF PSYCHO-NEUROSIS

Mentally
Obsession, e.g. with war service, racial and inter-marriage problems, fear of disease and death. Physical obsession, e.g. ritual slaughtering.

Somatically
Symptoms including nausea and vomiting, palpitations, trembling, sweating, micturition frequencies, diarrhoea.

Psychologically
Phobias, panics, dazed states, black-outs and general feelings of unwell. Disturbed emotions, e.g. crying without apparent cause.

the commencement of a neurosis, but especially in some of the elderly people there was no readily apparent reason. The way the neurosis manifests itself varied amongst the individuals.

The anxiety manifestations in some of the individuals of this pedigree are very similar to those described by Freud (1936) who, when discussing the more tenacious obsessional neuroses, gave instances of agoraphobia and fear of being alone, which were really expressions of a sexual nature. He pointed out that anxiety was a reaction to a situation of danger. Fears and phobias in the present pedigree range from inability to ride in buses or in trains, to refusal

to go under railway bridges for fear lest the bridge collapse. Where the condition is of anxious preoccupation, this is with fear of illness and obsession with death. These mental distresses are usually accompanied by psychosomatic disturbances. Table 4 gives a list of some of the commoner neurotic symptoms.

Two members of the pedigree show what can be interpreted as ritual obsessional psycho-neuroses which caused them some incapacity. They attended to early morning religious rites which are time consuming, and their whole lives were completely bound down by religious restrictions. One individual had low intelligence shown not only mentally but by physical appearance (III (3)), and the other (III (1)) was a life-long stammerer; neither married. These individuals were known as "religious fanatics" even by devout members of their family. Their obsessions with religious rites eventually found expression in their working as ritual animal slaughterers. Obsession with such rites cannot

TABLE 4. COMMON NEUROTIC SYMPTOMS (based on Miller (1947))

Disturbed sleep.
Headache.
Nervous dyspepsia—"gastritis".
Abdominal pain (mostly in women).
Vomiting.
Diarrhoea.
Micturition frequency (especially in men).
Palpitations.
Dysuria (in men).
Dyspnoea.
"Debility".
"Anaemia".
Gross tremulousness.

be completely attributed to their home life but must be in part determined by the particular type of neurosis they manifested. Such obsession with ritual procedures has its parallel in the routines of some schizophrenics. In this respect one may draw a comparison with what is known from current researches on Neurospora: different genes may eventually cause the same metabolic disturbances.

At first inspection the data appear to support the anticipation hypothesis, i.e., age of onset decreases with successive generations. Thus III (13) had his breakdown in his twenties, yet his affected daughter had hers before she was nineteen years old. Similarly, IV (2) underwent psychological investigation in her early thirties, while her affected daughter was hospitalized for psychosomatic disturbance at six years. However, there is no real support for anticipation as people more likely undergo psychological or hospital treatment now, and hence are recognised as neurotic; whereas before simply a change of scenery would have been suggested. Penrose (1949) has noted that in mental

illness of all diagnoses, mean age of onset of parents was 50.5 to 34.2 years in children for 1728 parent-child pairs.

The age of onset of neurosis is more difficult to assess, as so-called "highly-strung" children, e.g. IV (2), show it in a form of excitability, yet are not sufficiently ill to require a psychiatric treatment. Similarly, nowadays individuals may receive psychiatric treatment, whereas none was available before. The age of onset of neurotic disturbance with psychosomatic symptoms varies in the present pedigree from six to thirty years. It seems fairly certain that if a neurosis is to appear it will manifest itself before the individual is thirty. Thus although the time of genic action is variable, depending so much as it does on home environment, its appearance is limited to the earlier years of an individual's life. Unfortunately the pedigree contains no MZ twins for comparison, although the normal husband of II (7) remarried a non-neurotic second wife and had one son who is normal. This again supports the dominance hypothesis.

Now each generation of neurotics is born into a different environment from that of the previous generation; there may be more or less environmental stress. Also, there is greater likelihood of the neurotic personality being brought out by the environment of a neurotic family. If the neurotic had earlier been removed, possibly the same causes producing neurosis within both family and individual might not have been able to act on the latter. In the same way, it is often the very visitors to a patient in hospital who have brought about the stresses; it thus is imperative that those involved in setting up the neurosis should be kept at bay while the patient is returning to more normal behavior. Similarly, Lester (1947) also pointed out that a practitioner with a neurotic patient may really be up against a "family neurosis". Environmental effects of home surroundings and mental outlook of its inhabitants are very important in the manifestation, for instance, of hysteria and as an aid in unravelling causes of the neurosis. Such environmental effects have slowed down the recognition of the importance of inheritance in neurosis.

Slater (1943) found that neurotic and psychopathic tendencies were not associated with any particular birth order; this is confirmed in the present pedigree. Slater also found that activity of sexual life was associated with fertility. In the family of the propositus, persons of inactive sexual life came from (non-significantly) smaller sibships, whose members were relatively infertile to a significant extent. In family D only four out of eight sibs have married and only three children have been born. The relation between the proportion of sibs marrying and relative frequency of offspring shows here and supports Slater's contention.

Tronchin-James (1945) has pointed out that neurotics include not only persons of highest cultural and economic attainment, but also those of great

physical courage. The association of adverse circumstances, physical and mental, results in temporary breakdown, often some time after the event. He compared anxiety neurosis of these with hysteria: hysterics show a greater proportion of married people, have more children and marry younger than neurotics. In wartime neurotics are helped by giving them an insight into their condition. Thus Lord Moran (1945), when discussing effects of warfare on the manifestation of fright neurosis in shell-shocked soldiers, concluded that military candidates (in Britain) should undergo a psychological as well as physical medical test. This would save the wastage of many lives and pensions.

Davis (1947) disagrees that all individuals are more or less neurotic, or that clinical disorders are at the extreme of a distribution which includes the healthy. He considers that a neurosis begins when in a given situation increase in anticipating tension impairs adaptation, and when the vicious circle of increasing tension institutes decreasing attainment. Anticipatory tension, or its equivalent anxiety, may increase without the development of neurosis providing it does not impair powers of adaptation. Thus conflict, especially over sexual matters (e.g., IV (6)), can lead to psychosomatic breakdown. Maier (1948) was actually able to induce in rats convulsive seizures following wild activities, which eventually lead to a passive state. This abnormal behaviour arose from conflict in discrimination experiments, the rats being driven to respond to cards they had been trained to avoid. This, according to Maier, was considered as a conflict between doing and not doing, and was the condition which produced violent seizures most frequently. Unfortunately, no comparison was made of behaviour to the same conditions in different strains of rats, so that no genetical evidence of its inherited tendency is here available.

As Wolf (1948) has pointed out, psychosomatic medicine is concerned with bodily disorders related to problems of adjustment of personality and adverse life situations. There is evidence that an organism reacts to noxious events with a limited number of patterns of defence involving one or more organs, or organ systems. Even with vasomotor rhinitis it was possible to correlate most of the patient's episodes of nasal disease with periods of considerable emotional conflict. This may be true also for some cases of diabetes. It is possible in some patients to modify the morbid chain of events by sympathetic handling, and intelligent application to the individual's problems. It has become clear that mechanisms invoked by the human personality to deal with problems of adjustment may either underlie or modify disease. Behaviour patterns as seen in the above pedigree indicate how important are the pleiotropic effects of genes affecting personality. Miller (1947) also has drawn attention to the increasing recognition that emotional factors cause obscure physical symptoms, e.g. feelings of illness at times of stress, and that some conditions such as neurotic headache have a family history. These may run in families often by imitation,

but sometimes perhaps because of the presence of a "common structural substrate".

The neurotic personality therefore provides an excellent example of the interaction of nature and nurture, much of which can be separated by detailed analysis. By recognising the familial tendency of the condition, it should be possible for the physician to warn a family with the trait, to ease environmental stresses likely to produce a neurotic state in an otherwise normal individual. The old adage of *mens sana in corpore sano* is not absolutely true: it is perhaps just as correct to say "a healthy body from a healthy mind". A neurotic personality is an individual's inability to adapt himself to a certain environment, regardless of whether this be sexual or non-sexual, because it is not that most congenial to him. This provides strong support for Darlington's (1953) hypothesis that human beings genetically assort themselves into the types of environment they prefer. In this respect heredity is much stronger than hitherto suspected in determining that individuals of similar temperament and outlook, or in occupational capacity, tend to come and remain together. Here again this hypothesis is borne out by considerable improvement being obtained for some neurotics (perhaps recombinations or cross-overs) by breaking them away from family ties and giving them new, more congenial surroundings. This means placing them in the kind of environment which they prefer and for which they are genetically determined.

SUMMARY

Previous studies on psycho-neuroses have depended on statistical estimates to show their genetical basis, and to circumvent the powerful influences of environment. Following an historical literature survey, case reports are given of neurotics in the pedigree of a large Anglo-American Jewish family. These show the various ways a neurotic pattern manifests itself. Predisposition to neurotic symptoms is inherited as an autosomal dominant in this family. There were no psychoses in the family.

The manifestations of psycho-neurosis are traced through five generations. Males and females are equally likely to be affected, but males seem to be more severely afflicted. The basic environmental causes, sexual and non-sexual, contributing to the onset of psycho-neurosis are analysed. Conflict, e.g. over religious and sexual matters, and fear of loss of security and sexual object are important elements in starting a psycho-neurosis. Sometimes there is no apparent cause.

There is no support for anticipation, nor for any birth order, but there is a relation between proportion of sibs marrying and relative frequency of their offspring. Clinical aspects are also considered, such as the commoner psychosomatic disturbances associated with the neurotic personality. Neurotics may

show considerable improvement following removal from their causative surroundings.

ACKNOWLEDGMENT

The writer wishes to thank Dr. W. McIntyre for his interest and encouragement in this work.

REFERENCES

BROWN, F. W. 1942. Heredity in the psychoneuroses. *Proc. R. Soc. M.*, Lond. 35: 785–790.

DARLINGTON, C. D. 1953. *The Facts of Life*. London: Allen and Unwin.

DARWIN, C. 1873. *The Expression of the Emotions in Man and Animals*. London: John Murray.

DAVIS, D. R. 1947. Disorders of skill: an experimental approach to some problems of neurosis. *Proc. R. Soc. M.*, Lond. 40: 583–84.

DIEM, O. 1905. Die psycho-neurotische erbliche Belastung der Geistesunden und der Geisteskranken. *Arch. f. Rass. Biol.* 2: 215–252.

EYSENCK, H. J. & PRELL, D. B. 1951. The inheritance of neuroticism: an experimental study. *J. Ment. Sc.*, Lond. 97: 441–65.

FREUD, S. 1933. *New Introductory Lectures on Psychoanalysis*. London: The Hogarth Press.

FREUD, S. 1936. *Inhibitions, Symptoms and Anxiety*. London: The Hogarth Press.

GATES, R. R. 1946. *Human Genetics*. Vol. 2. New York: Macmillan & Co.

GEBBING, M. 1932. Die Erbanlage bei neurotikern. *Deut. Zschr. Nervenh.* 125: 45–85. (Seen in Gates.)

GUNTHER, M. & PENROSE, L. S. 1935. The genetics of epiloia. *J. Genet.*, Cambr. 31: 413–430.

HYDE, R. W. & CHISHOLM, R. M. 1944. The relation of mental disorders to race and nationality. *N. England J. M.* 231: 612–18.

KALLMANN, F. J. 1950. The genetics of psychoses. *Am. J. Human Genet.* 2: 385–390.

LESTER, W. 1947. The hysteric in general practice. *Practitioner*. 158: 425–432.

MAIER, N. R. F. 1948. Experimentally induced abnormal behaviour. *Sc. Month.* 67: 210–216.

MCINNES, R. G. 1937. Observation on heredity in neurosis. *Proc. R. Soc. M.*, Lond. 30: 895–904.

MILLER, H. G. 1947. The recognition of neurotic illness. *Practitioner*, Lond. 159: 128–35.

MORAN, LORD. 1945. *The Anatomy of Courage*. London: Constable.

NEWMAN, H. H. 1933. The effects of hereditary and environmental differences upon human personality as revealed by studies of twins. *Am. Natur.* 67: 193–205.

PASKIND, H. A. 1933. Heredity of patients with psychasthenia. *Arch. Neur. Psychiat.*, Lond. 29: 1305–1317.

PENROSE, L. S. 1948. The problem of anticipation in pedigrees of Dystrophia myotonica. *Ann. Eug.*, Cambr. 14: 124–132.

PENROSE, L. S. 1949. *The Biology of Mental Defect*. London: Sidgwick & Jackson.

PETRIE, A. A. W. 1941. Reconstruction in psychiatry. *Proc. R. Soc. M.*, Lond. 35: 569–576.

ROSS, T. A. 1943. *The Common Neuroses*. 2nd ed. London: E. Arnold.

SLATER, E. 1935. The incidence of mental disorder. *Ann. Eug.*, Cambr. 6: 172–186.

SLATER, E. 1943. The neurotic constitution. A statistical study of two thousand neurotic soldiers. *J. Neurol.* 6: 1.

SLATER, E. 1943–5. A demographic study of a psychopathic population. *Ann. Eug.*, Cambr. 12: 121–137.

SLATER, E. & SLATER, P. 1944. A heuristic theory of neurosis. *J. Neur. Neurosurg., Psychiat.* N.S. 7: 49–55.

SNYDER, L. H. 1947. Human heredity. In *Genetics, Medicine and Man.* Ithaca, N. Y.: Cornell University Press.

TRONCHIN-JAMES, R. N. 1945. Sociological aspects of psychoneurosis. *Practitioner*, Lond. 159: 307–311.

WOLF, S. 1948. Experimental research into psychosomatic phenomena in medicine. *Science.* 107: 637–639.

Distribution of Blood Groups Among the Eskimos, Indians, and Whites of Western Alaska[1]

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EVER SINCE L. and H. Hirszfeld discovered during the first World War that the frequency of the four blood groups (A, B, O, and AB) varied in the different peoples of the Balkans, and that this variation was related to racial origins, geneticists and physical anthropologists have utilized this new tool in the study of "races." The discovery of other blood groups, namely the M-N and the Rh types which are unrelated to the ABO groups has further enhanced the value of this new tool.

The object of this paper is to present some preliminary findings pertaining to blood variations among the Eskimos, Whites, and Indians of Western Alaska. Previous studies on these peoples have been limited to those made by W. S. Laughlin in 1949 on the Aleuts; V. E. Levine in 1938 and 1944 on Eskimos in the Barrow and Nome areas; and G. A. Matson in 1947 on the Eskimos of the Kuskokwim Basin. The present study covers a large group of Eskimos along the Bering Sea and Arctic Ocean coasts and Indians of the Interior.

We wish to stress here that the materials presented in this paper are preliminary. They are presented now only because the full study will require another two or three years for final completion, and because it seems probable that a preliminary report at this time may be of some interest and value to others.

The present material covers the results on a total of 5,205 individuals from villages in the Kotzebue Sound, Norton Sound, Lower Yukon, Kuskokwim Basin, Nushagak Bay, and Bering Sea areas, and in Interior Alaska. For comparative purposes data on Whites were obtained from areas covered in the BCG program and the community-typing programs in Fairbanks and Palmer, Alaska.

Late in 1948 the Alaska Department of Health established a program of BCG vaccination in areas reporting a high incidence of tuberculosis. Since the BCG teams were visiting all of the remote areas, a serological survey for syphilis was added to the routine BCG program. Realizing that this was a unique opportunity to obtain blood specimens for special study, and that the results

Received November 5, 1952.

[1] Presented before the Second Alaskan Science Conference McKinley Park, Alaska, September 1951.

would be of value to geneticists, anthropologists, sociologists, and ethnologists, Dr. C. E. Albrecht, Commissioner of Health of the Alaska Department of Health, and Mr. R. B. Williams, Director of the Division of Public Health Laboratories, suggested that all available data on blood factors be extracted from the blood specimens. A program was carefully set up with this goal in mind.

The blood-typing program served several purposes: first, it encouraged more individuals to be blood-tested, giving a wider coverage for the VD survey; second, the individuals were furnished identification cards showing ABO and Rh blood types; third, it gave the Alaska Native Service Hospitals a "walking blood bank" for their areas; and fourth, it provided data for the present study and should continually provide data for new or extended studies.

The BCG nurses were carefully instructed as to the designation of race. Only putative Indian and Eskimo full-bloods were listed by race name. All admixtures were listed as such, showing the degree of admixture with White, if known. The nurses checked with the local teachers, missionaries, or Alaska Native Service Field Nurses when there was any question whether a given individual was full-blooded. Blood specimens were collected by venipuncture on persons 14 years of age or over, and forwarded to the Anchorage District Laboratory via air express.

The blood specimens were serologically checked for syphilis and the clots were used for blood-typing. Each specimen was tested for ABO blood group and Rh_o (D) type, and when possible, for sub-groups of A and for the M and N types by slide tests. Rh negatives were checked by tube test. All the A-B and Rh sera were obtained from the American Hospital Supply Company; M-N sera from Lederle Laboratories; and absorbed B serum from Certified Blood Donor Service, Jamaica Plains, N. Y.

A total of 5,205 specimens of blood were tested: 2,954 Eskimo, 333 Indian and 1,621 White; the others were from members of mixed race. For comparative purposes the frequencies of ABO groups among the Indians of Southeastern Alaska are shown in two of our tables. The data for Southeastern Alaska were obtained from R. B. Williams, Juneau, Alaska, who is conducting a similar study among the Tlingits of that area.

Tables 1–4 present the frequencies of the different blood groups and blood types among the different peoples which were studied and the gene frequencies which were calculated from these group frequencies. Since this report is only a preliminary one we shall not enter into any detailed discussion of differences and similarities, but we do wish to call attention to a few variations in the blood group frequencies of the groups and to comment briefly on their probable meanings.

The frequency of blood group A among the racial groups studied ranged from 36.34% (Indian) to 44.08% (Eskimo). Among the Whites it was found to be

TABLE 1. FREQUENCY OF BLOOD TYPES IN SPECIFIED RACIAL GROUPS IN WESTERN ALASKA

RACIAL GROUP	NO. TESTED	PERCENTAGE DISTRIBUTION OF TYPES				FREQUENCY OF GENES		
		A	O	B	AB	$I^A(p)$	$I^B(q)$	$i(r)$
White	1621	42.66	43.29	10.12	3.93	.2691	.0728	.6579
Eskimo	2954	44.08	38.08	13.08	4.77	.2878	.0974	.6146
Indian	333	36.34	60.96	2.40	0.30	.2048	.0169	.7783
Indian-White	39	38.46	53.85	5.12	2.56	.2281	.0342	.7376
Eskimo-White	258	40.73	41.86	13.18	4.26	.2605	.0949	.6445
Tlingits*		24.2	75.8					
White (US)†	141,774	40.77	45.55	9.96	3.72			

* Study of Tlingit, Haida and Southeastern Alaska Natives—R. B. Williams, Personal Communication. Figures may vary from final results.

† Studies of Hervey-Diamond—National Blood Program.

TABLE 2. FREQUENCY OF SUB-TYPES OF A AND AB IN SPECIFIED RACIAL GROUPS IN WESTERN ALASKA

RACIAL GROUP	TOTAL A + AB	A_1		A_2		A_1B		A_2B	
	No.	No.	%	No.	%	No.	%	No.	%
Eskimo	748	686	100	0	0	62			
White	189	133	76.8	40	24.2	10	62.5	6	37.5
Eskimo-White	56	39	82.9	8	17.1	7	77.7	2	22

TABLE 3. FREQUENCY OF M N TYPES IN SPECIFIED RACIAL GROUPS IN WESTERN ALASKA

RACIAL GROUP	NO. TESTED	PERCENTAGES			FREQUENCY OF GENES	
		M	MN	N	A_g^M	A_g^N
White	784	36.61	45.03	18.37	.605	.4285
Eskimo	604	63.91	30.46	5.62	.799	.237
Indian	17	58.82	35.29	5.88	.768	.2419
Eskimo-White	119	44.53	41.18	14.29	.667	.377
Tlingits*		73.3	26.67	0		

* Study of Tlingit, Haida, and Southeastern Alaska Natives.—R. B. Williams, Personal Communication. Figures may vary from final results.

TABLE 4. FREQUENCY OF RH FACTORS IN SPECIFIED RACIAL GROUPS IN WESTERN ALASKA

GROUP	NO. TESTED	Rh+		Rh−	
		No.	%	No.	%
White	1371	1312	83.51	259	16.49
Eskimo	2522	2521	99.96	1	0.04
Eskimo-White	156	153	98.08	3	1.92

42.66%; among Indian-White 38.46%; and among Eskimo-White 40.73%. The Tlingits of Southeastern Alaska studied by R. B. Williams showed a low frequency of A, namely 24.2%.

The frequency of blood group O ranged from 38.08% (Eskimo) to 60.96%

(Indian). The Eskimo-White had a higher percentage of O (41.86%) than the Eskimo, and the Indian-White a lower percentage (53.85%) than the Indian. The Tlingits had the highest percentage of O (75.8%); the Whites an intermediate one (43.29%).

The Eskimo-Whites had the highest percentage of blood group B (13.18%) with the Eskimo next (13.08%). The Whites had 10.11% and Indians 2.40%. The high percentage of B among the Eskimos of Alaska had been noted previously by Matson and Laughlin. Type B has not been reported among the Tlingits of Southeastern Alaska.

The Indian had the lowest incidence of blood group AB (0.3%); the Eskimo the highest (4.77%) and the Whites (3.93%). Type AB has not been found among members of the Tlingit group.

Of 748 Eskimos, of group A and AB combined, who were tested for subtypes of A, all or 100% were A_1 or A_1B. In contrast to this, 189 A or AB Whites gave 24.2% belonging to sub-type A_2. Of 56 Eskimo-Whites of group A and AB, who were tested, 17.1% were sub-type A_2.

Of the 1,524 specimens tested for M-N blood types the Eskimo and Indian showed the lowest incidence of N, (5.62% and 5.88% respectively), compared to the Eskimo-White (14.29%) and White (18.37%). Correspondingly the incidence of M was high in the Eskimo and Indian: 63.91% and 58.82% compared to the White incidence of 36.61%.

The Eskimos were 99.96% Rh positive. Only one out of 2,522 Eskimos was Rh negative, and though records indicate that this individual was a full-blooded Eskimo, there remains the possibility of admixture with White. In contrast to the Eskimos, the Whites were only 83.51% Rh positive; of the 156 Eskimo-White who were tested, 98.08% were Rh positive.

SUMMARY

1. The blood of a total of 5,205 individuals belonging to specified racial groups in Western Alaska were tested for ABO types. The Eskimo group had the highest frequency of Types A, B, and AB, in contrast to the low frequency of A, B, and AB among the Indians (Tinneh) of the Interior. The frequencies of ABO types in the Indian-White group differed from those of the Indian sample, and approached more closely the frequencies of the ABO types among the Whites. The same observation applies to the Eskimo-White sample.

2. The variation in the frequency of blood type A among the racial groups was not as great as were those for B, O, and AB.

3. Variations in the frequencies of the ABO groups among the Eskimos in six geographic areas were noted, but of these, only the variation in the frequency of group B was marked. The Eskimos of the Nushagak area has the highest frequency (19.8%) of B, and the Eskimos of the Kotzebue Sound had the lowest (10.3%). Of special interest is one group from Hooper Bay, not included in our figures. It had a frequency of 37% type B.

4. The Eskimos showed a complete absence of blood group A_2 compared to a percentage of 24.2 within all A and AB groups among the Whites, and 17.1% among Eskimo-Whites.

5. In Eskimos and Indians the incidence of N type was 5.6% and 5.88% respectively, compared to the White incidence of 18.37%.

6. Ninety-nine and ninety-six hundredths per cent (99.96%) of the Eskimos were Rh positive, i.e. only 1 Eskimo out of 2522 was found to be Rh negative.

7. An observation of extreme interest was that mixtures of Eskimo or Indian with White were observed, but in areas on both the Yukon and Kuskokwim Rivers where the Eskimo and Indian meet, and where trade and the villages are close together, exceedingly little Eskimo-Indian mixture was noted. In other words, our findings indicate that there has been very little genetic mixture of the races in the Eskimo-Indian border areas.

8. There have been frequent comments that the Eskimos of the Bering Sea areas were not full-blooded and had mixed with other peoples, particularly the White. This conclusion has been based on the fact that the ABO frequencies among the Eskimos closely correspond to those of the Whites. If this be true one should have expected to have found a small percentage of sub-type A_2, a high percentage of type N close to that of the Whites, and the presence of Rh negative among the natives. We found none of these. Hence our findings indicate that these Eskimos have not mixed with the Whites to any appreciable extent.

9. From the data presented here and other data on file in our laboratory but not yet reported, a great deal of information has been gained on the distribution of blood groups among the native races of Alaska and among the racial admixtures. We hope in future studies to present the blood groups and gene frequencies among tribal or dialectal groups covering a period of two or three generations. Further studies are also indicated on the Indians of Interior Alaska and the Eskimos of St. Lawrence Island, as well as the people of the border regions where questions exist relative to Eskimo-Indian admixture.

REFERENCES

Boyd, William C. 1950. *Genetics and the Races of Man.* Boston: Little, Brown & Company.

Hervey, G. W., Diamond, L. K., & Watson, V. 1951. Geographic blood group variability in the United States. *J. Am. M. Ass.* 145: 80–81.

Laughlin, W. S. 1951. *Papers on the Physical Anthropology of the American Indian.* New York: The Viking Fund.

Levine, V. E. The blood groups in Eskimos (quoted from Matson and Laughlin).

Matson, G. A. & Roberts, H. J. 1949. Distribution of the blood groups, M-N and Rh types Among eskimos of the kuskokwim basin in western Alaska. *Am. J. Phys. Anthrop.* 7 n.s. (1) 109–122.

Race, R. R., & Sanger, Ruth 1950. *Blood groups in man.* Springfield: Charles C Thomas.

Wiener, A. S. 1943. *Blood groups and transfusion* (3rd Edition), Springfield: Charles C Thomas.

Williams, R. B. 1951. Personal Communication.

On the Inheritance and Development of Clinodactyly

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IN MAN, as in other animals, the external characteristics of the integumentary system are the most easily studied from the genetic point of view. And many such traits are known (Cockayne, 1933). The most easily studied internal system is obviously the endoskeleton, since it determines the shape and form of the organism and any change or modification of it is readily noticed. In the case of the skeleton, as no doubt in other organ systems, most hereditary differences are dependent upon multiple factors. The gradational variability in the absolute and relative size of the bones and parts of the face is unquestionably the genetic basis for the inexhaustible variety of the human countenance. There is considerable gradational variability also in the skeleton of the appendages as shown by the radiological examination of twins and triplets (Buschke, 1935).

Of the many hereditary skeletal defects which stand in sharp contrast to the normal, only a relatively few involve the skull, while the overwhelming majority affect the skeleton of the appendages. A possible explanation is that any considerable change in the skull might be lethal. However, there is another possibility. It is well known that many mutants affect the bristles in Drosophila melanogaster and other species while this is not the case in D. hydei (as shown especially by Spencer, 1949), although the latter species has also been extensively studied from the genetic point of view. Briefly, it happens that all parts of the organisms are not equally plastic and this, although a problem in genetics and evolution, is still largely unsolved, (see discussion by Muller, 1949). Its solution, no doubt, awaits a more detailed knowledge of how genes act and interact to produce their effects. In addition to ease of detection, the mutant traits of the skeleton, in contrast to other internal traits, can be most readily studied by the X-ray technique to obtain considerable knowledge in developmental terms of how the genes act. And this can be supplemented by the present high state of knowledge on the histogenesis of bone.

Received April 16, 1953.

The following report is on clinodactyly, or "crooked little fingers". It attempts to analyze all the available data to determine the mode of inheritance and secondly to discuss the trait from a developmental point of view. This task is facilitated by the publication (Bell, 1951), of a monograph on hereditary digital anomalies and by the radiographic atlas of standard plates of normal development of hand and wrist by Greulich and Pyle (1950) from birth to complete maturation of the skeleton.

Of the many forms of digital anomalies reported in the literature the bone deformity in the middle phalanx of the fingers is among the most prevalent. Moreover, the deformity in the middle phalanx of the 5th finger appears less variable than some other digital anomalies, and so has been proposed as one of the more favorable traits for linkage studies in man.

In the monograph mentioned Bell has made a classification of the various types of brachydactyly and classifies as A_3 the trait discussed here. It involves a shortening of the middle phalanx of the 5th finger, especially on the radial side, which in turn leads to a radial deflection of the terminal phalanx, while the remaining digits are normal. These cases should not be confused with other types of crooked little fingers as presented by Hefner (1924, 1929, 1941), Koenner (1924), Moore and Messina (1936), and Stoddard (1939).

We have observed at least two cases in which the radial inclination of the fifth digit included the two terminal phalanges instead of only the terminal phalanx. These cases are not included in the following analysis. Bell's pedigree #17 is also not included in the pooled data discussed below. Although she classifies it under her type A_3, yet it is clearly not a case of uncomplicated clinodactyly, since syndactyly as well as unilateral manifestation are involved.

THE DATA

The pedigrees collected and recorded by us (Figure 2) were made by a visual inspection of the hands. In five individuals the trait was recorded by correspondence. In every case we made certain that only the little finger was involved and that the curving was radial. Moreover, we made certain that this bending began from the interphalangeal joint of the middle and distal phalanx, i.e., the distal phalanx was tilted radially. The majority of the cases of clinodactyly are readily identifiable. If there is a doubt as to whether or not the case is clinodactylous, one can be almost entirely certain that it is not. It is somewhat like dwarfism. If there is doubt as to whether a person of short stature is a dwarf, the probability is overwhelming that he is simply at the extreme low end of the curve of normal variability. As a matter of record a large number of normal little fingers which have been observed by us have some slight degree of radial curvature. Clinodactyly produces no impairment on the movement of the hands. Further, X-ray sudies of some of these cases show that all of the rest of the phalanges of the hands are normal.

The normality was determined merely by inspection in a comparison with the radiographic atlas mentioned. There is at present no standard series of measurements of sizes and angles of inclination for the phalanges of the normal hand

Figure 1 shows a photograph of a typical case of clinodactyly. These hands belong to one of the identical male twins illustrated in Figure 2, case D, II 5. In Figure 1, notice that the degree of curvature is remarkably uniform in both little fingers. The distal phalanx inclines radially, forming an angle of nearly 20°. The degree of radial curvature may be determined by the angle formed between the mid-longitudinal line of the distal phalanx and the mid-longitudinal

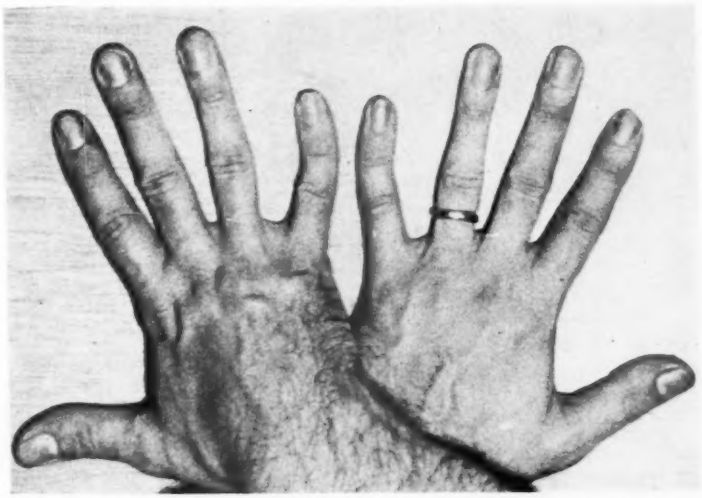

FIG. 1. Photograph illustrating a typical case of "crooked little fingers" or Clinodactyly. The left and right hands of this individual have been crossed to facilitate the comparison of the radial curvature in the two little fingers.

line passing through middle and proximal phalanges. Angle measurements made from the three X-ray photographs are undoubtedly much more accurate and range from 15° to nearly 30°. No attempt was made to collect other associated traits in these individuals. However, webbed toes occur between the 3rd and 5th digit in both identical twins and in the daughter in Figure 2, case D, II-4 and 5, III-2.

Figure 3, *A* and *B*, illustrates two X-ray photographs taken of the hands of two sisters found in case E, II-1 and 2, (Figure 2). *A*, was about 20 years old and *B* was about 10 years old. In *A*, the older girl, all of the phalanges of both hands are normal except for the middle phalanx of the 5th finger. This phalanx is slightly shorter on the radial side, forming a visible slanting on its upper

surface. As a result of this slanting, the normal distal phalanx sets in a radial inclined position. The hands of her younger sister, *B*, clearly show all normal phalanges with their respective unfused epiphyses, a condition which is normal

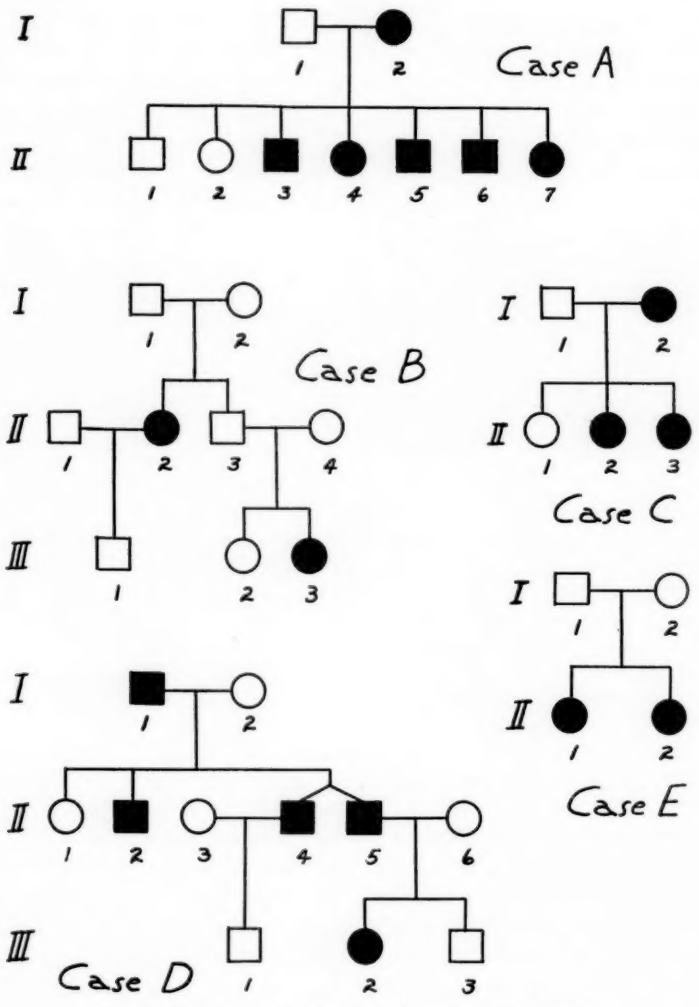

FIG. 2. Pedigrees of "crooked little fingers" or Clinodactyly

for children of this age, except for the middle phalanx of the 5th finger. Here we note an under-developed ossification area on the upper radial position of each of these phalanges. Figure 4 *B*, an enlargement made from Figure 3 *B*,

illustrates this condition more clearly. The arrows point at the unossified areas on the radial side of each middle phalanx of the 5th finger. These areas appear

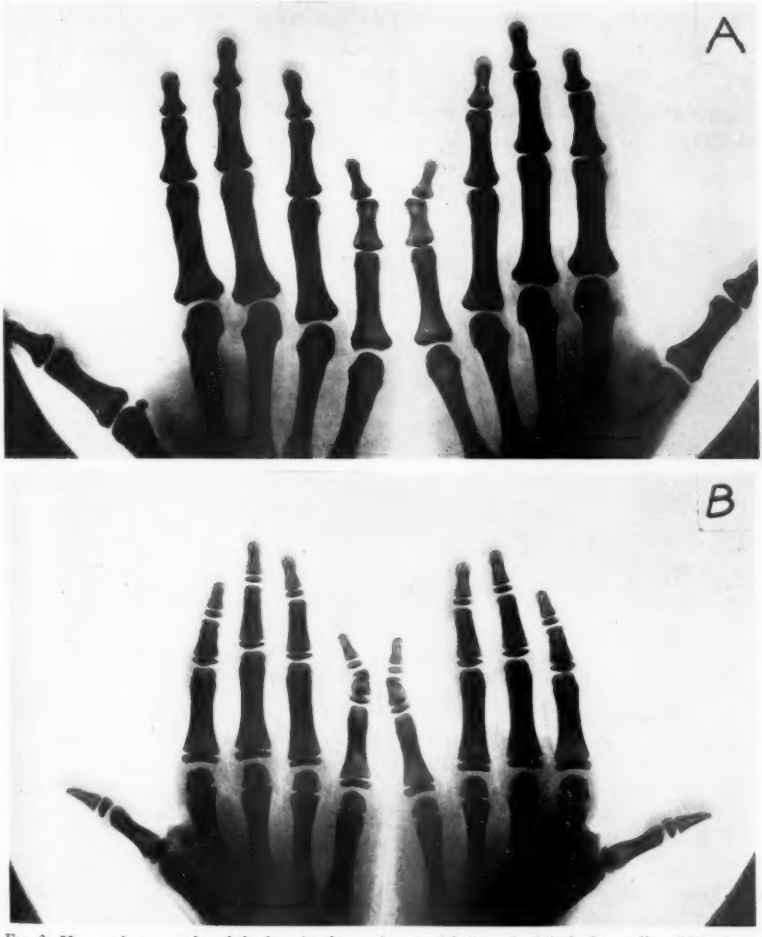

FIG. 3. X-ray photographs of the hands of two sisters with "crooked little fingers" or Clinodactyly. The older sister, *A*, is about 20 years of age. The upper surface of the middle phalanx of both little fingers is slanted radially causing the distal phalanx to incline radially. *B*, the 10-year old sister shows similar inclination of the little fingers. Note the underdeveloped ossification area in the middle phalanx of both little fingers. (See Figure 4, *A* and *B* for detail views).

to be still in a cartilaginous stage. Figure 4 *A* shows a radial view of the left and right "crooked little fingers" of the 20 year old sister. The ossification of these areas is already completed at this age. This view, 4 *A*, also shows that the inclination is not of the flexion type.

These facts seem to indicate that clinodactyly is a definite case of developmental arrest of the ossification center. This slowing-down process of ossification might possibly begin at any time after the ossification center appears during the embryonic life and extend well beyond 10 years of age. Moreover, this arrest is restricted to a definite area of the middle phalanx of the 5th finger.

Figure 5 illustrates a variation of clinodactyly. Figure 5 *A* shows an X-ray photograph of the hands of a 4-year old girl with a definite but mild case of clinodactyly. She is the daughter of one of the identical twins with clinodactyly,

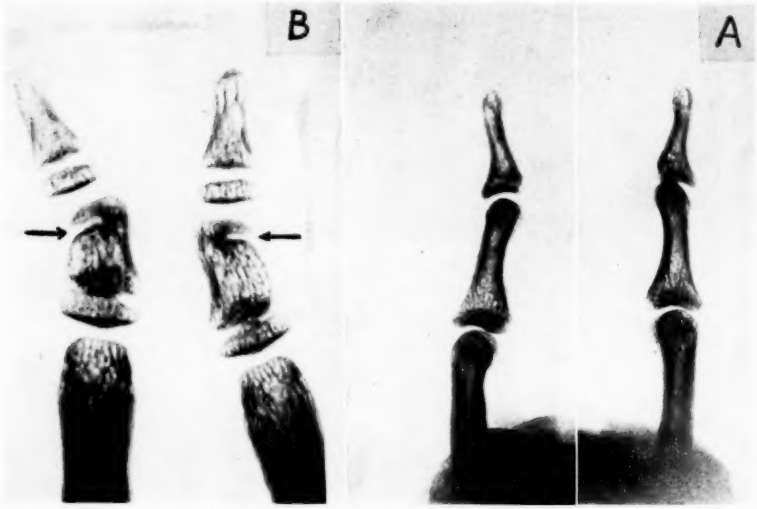

FIG. 4. X-ray photograph enlargements, *A*, radial view of the left and right "crooked little fingers" of the 20-year old girl. Notice there is no inclination in the direction of flexion. *B*, shows the left and right "crooked little fingers" (5th) of the 10-year old sister. Note the underdeveloped ossification area in the upper radial region of the middle phalanx (pointed out with arrows). For complete view of the hands see Figure 3, *A* and *B*.

illustrated in the pedigree chart in Figure 2, case D, III-2. As one can see the radial bending of the little finger in this 4-year old is not as severe as the 10-year old illustrated in Figure 3 *B*. A detail view of the two little fingers, Figure 5 *B*, shows that the ossification of the upper radial area of each middle phalanx is already completed, while in the 10-year old this area is still in cartilage stage. The only evidence we see is a small dent in each of these phalanges as pointed out by arrows in Figure 5 *B*. It seems evident, therefore, that in clinodactyly the degree of radial bending is related to the length of the period of delay of the ossification process. In the 10-year old girl the radial bending is quite severe and the ossification is not complete, while in the 4-year old the bending is much

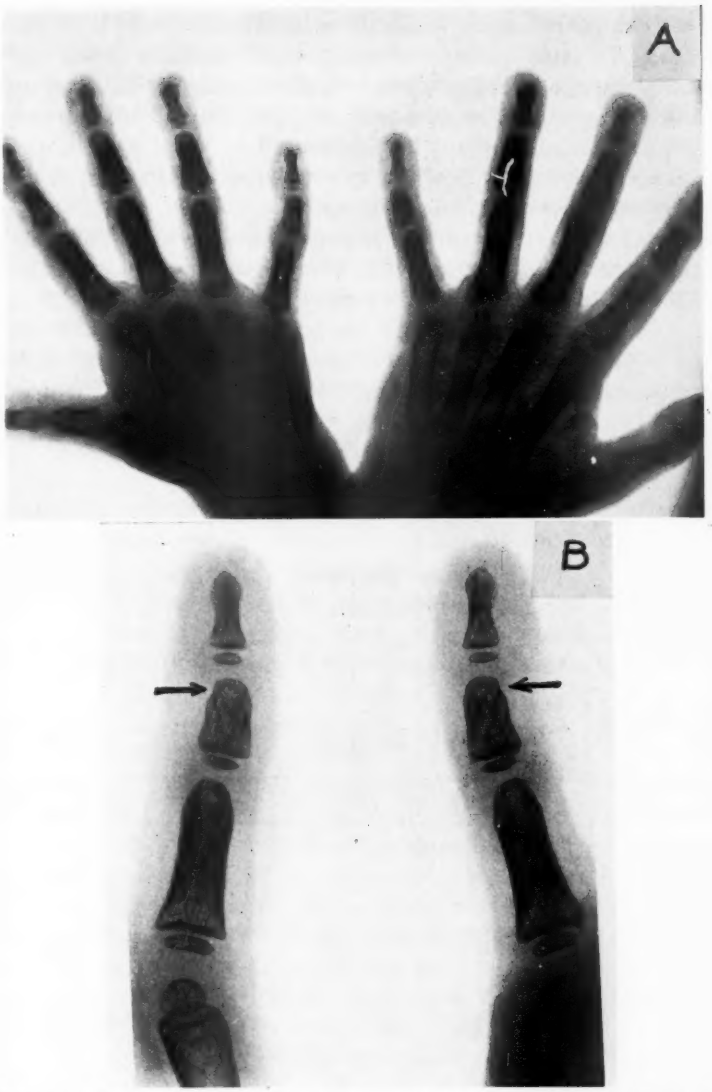

FIG. 5. X-ray photographs of the hands of a 4-year old girl with a mild case of clinodactyly. *A*, complete view of the left and right hands, showing a slight but definite radial bending of the little fingers. As seen in *B*, a detailed view of the two little fingers, the ossification of the upper radial area of the middle phalanges is already completed, only a small dent (pointed out by arrows) is seen in the radial region of these two phalanges.

less severe and the ossification is already completed. One might naturally have expected that the X-ray picture for the 4-year old would show a still

earlier stage in the incomplete ossification. But as mentioned this is definitely not the case. The possible explanations for this from a genetic point of view are first that multiple alleles may be involved, or secondly, that genes at different loci are concerned, or perhaps most plausibly, the effect is one of several modifying factors, which would at the same time explain the slight lack of penetrance. Clearly no decision can be reached on the basis of the present data and observations.

In determining the mode of inheritance of clinodactyly we have combined our data with those presented by Bell (1951) as A_3-type, except for her pedigree #17. They are listed in Table 1. The combined data involve 15 pedigrees with a total of 51 sibships. Analysis by inspection of the pedigrees indicates that this trait is an autosomal dominant. There are 4 instances in which neither parent shows the trait, denoting a slight lack of complete penetrance. In all

TABLE 1. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTATION ON BASIS OF SIMPLE AUTOSOMAL DOMINANT (1:1 RATIO)

SIZE OF SIBSHIP (z)	NO. OF SIBSHIPS (n_z)	TOTAL SIBS (zn_z)	AFFECTED SIBS (r)	CORRECTIVE FACTOR (f)	EXPECTED AFFECTED (fn_z)	VARIANCE (s^2)
1	10	10	10	1.000	10.000	—
2	12	24	16	1.333	15.996	2.666
3	10	30	20	1.715	17.150	4.898
4	5	20	14	2.134	10.670	3.911
5	3	15	11	2.581	7.743	3.246
6	2	12	6	3.047	6.094	2.758
7	5	35	25	3.527	17.635	8.335
9	1	9	7	4.509	4.509	2.215
10	3	30	17	5.005	15.015	7.434
Totals	51	185	126	—	104.812	35.643

$s = \pm 5.95$.

other cases only one parent is affected. Numerical tests applied on the pooled data listed in Table 1 show unusual results. In spite of the small lack of penetrance there are significantly more affected than expected on the basis of a 1:1 ratio, even after applying the corrective factor (Hogben, 1946) for small family size. The difference between the 126 observed affected and the 105 expected affected is 21, while the standard deviation is slightly under 6. This significant difference might most plausibly be explained if the early published pedigrees were reported merely because of the unusually large number affected.

Also an attempt was made to find the frequency with which clinodactyly occurs in the population, in order to determine the gene frequency. In a study of Heberden's nodes (enlargement of the terminal joints of the fingers owing to hypertrophic arthritis) over the years (Stecher, 1940) and one which is still continuing, there was a total of 4304 white patients over 20 years of age ex-

amined at the City Hospital of Cleveland. Of these 2117 were men and 2187 were women. Only 4 cases of clinodactyly were found; of these 3 were men and one a woman. Although these data do not give an ideal cross section of the population, yet they nevertheless give an indication of the incidence of clinodactyly in the population of Northern Ohio. From these data the incidence of clinodactyly may be taken as approximately 1 in 1,000. Consequently, assuming random mating and genetic equilibrium, the frequency of *d*, the dominant gene for clinodactyly has a frequency of 0.0005 and for the normal recessive allele *r*, the frequency is 0.9995. The incidence of heterozygotes in the population is nearly 1 in 1,000. The homozygotes would be expected to occur about 1 in 400,000.

It perhaps should be pointed out that the pedigrees and the numerical test are in agreement with the hypothesis that clinodactyly is a simple autosomal recessive trait. On this basis then with the incidence in the population of 1 in 1,000, the frequency of the recessive gene is 0.032 and for the dominant normal allele the frequency is 0.968. Consequently the frequency of heterozygotes in the population is 0.06 or about 1 in 16. With the population mating at random in regard to clinodactyly then about 1 in 256 marriages should be between heterozygotes and about 1 in 4 of these families would have affected children, i.e. approximately 1 in 1024 marriages. In the 51 sibships there were 4 with neither parent affected. Clearly, on these grounds, the data overwhelmingly favor the conclusion that clinodactyly is an autosomal dominant with a slight lack of penetrance.

DISCUSSION

Clinodactyly should be clearly distinguished from other types of crooked little fingers in that clinodactyly specifically affects the bone formation of the middle phalanx of the 5th finger in a manner that it inclines radially. All other cases of crooked little finger as reported in the literature should be clarified and properly classified at this point. From the study of our data as well as the data presented by Bell (1951), Hefner (1924, 1929, 1941), Koenner (1924), Moore and Messina (1936), Stoddard (1939), and Pol (1921), it seems clear that the inherited types of crooked little fingers may be classified into three general categories; (1), those due to *incomplete ossification*, (2) those due to *abnormal tendons*, and (3) those caused by *fused ossification*. For example, the incomplete ossification type may well be represented by our data as well as those of Pol (1921); the abnormal tendon type may be represented by Hefner's cases, and the fused ossification class by Koenner's data. These three general categories may well apply in classifying digital anomalies of the other fingers. In our opinion this proposal of the method of classifying digital anomalies has the distinct advantage over the method suggested by either Bell (1951), or Stoddard (1939) in that this method is more inclusive. Practically all of the

different forms of hereditary digital anomalies may be classified under any one of the three categories or combination of them.

The previous analysis clearly leads to the conclusion that clinodactyly is inherited as a simple autosomal dominant. Furthermore, X-ray observations indicate that clinodactyly is a trait which seems to be brought about by a slowing-down process of ossification, specifically in the upper radial area of the middle phalanx of the 5th finger. This slowing-down process might be interpreted from two points of view; (1) as a direct arrest of the bone-forming process, or, (2) as a delay in the orderly transformation of the cartilage cells. According to the first point of view, this arrest may be caused by either a local failure in the supply of the bone minerals, or by a delay in the production of phosphatase in the osteoblasts. This delay extends for quite a long period of time. It may possibly begin sometime after the 83rd day-old embryo and extend well beyond the 10th year of age. Mall (1906) in studying the early human embryos with regard to the time of the appearance of the ossification centers in the phalanges, stated that "the second row are the last phalanges to appear. On the 75th day the center in the second phalanx is well-formed and those of the third and fourth phalanges are each represented as two very small nuclei, the one on the radial side being a little longer than the one on the other side. On the 83rd day a single center appears in the fifth phalanx. It is crescent-shaped with its closed side outwards and the open side directed towards the radial side of the hand. It retains this form, growing only in size in embryos up to 105 days old." If we are permitted to use Mall's embryological observations in further interpreting our results on clinodactyly, then it means that this trait is a result of a developmental arrest of the ossification center of the middle phalanx of the 5th finger.

According to the second point of view, this arrest may be caused by a delayed reaction in the transformation of the cartilage cells. Streeter (1951), in studying the development of the human embryonic humerus during its cartilaginous period, observed that cartilage cells, as they grow older pass through an orderly series of transformations. He recognized five phases. These begin with a proliferation and growth of cells, followed by an extensive vacuolization of their cytoplasm and immediately followed by a formation of intercellular substance, and finally, ending with a liquefaction of disintegration of the cells. The end of this last phase is followed by an invasion of cells derived from the inner coating of the periosteum. These cells progressively fill in the zone of disintegrated cartilage cells, thus transforming the cartilage into marrow and bone. Although these observations were restricted to the development of the humerus, Streeter is of the opinion that all other skeletal parts (endochondral ossification) follow the same basic sequence. He believes that "the chief difference in the manner of their development rests in the extent to which a cartilaginous period intervenes between the primitive mesoblastic tissue and the definitive bony struc-

ture." In genetic terms, the dominant gene for clinodactyly produces its effect by delaying some physiological process in the orderly series of transformations of the cartilage cells, specifically localized in the upper radial region of the middle phalanx of the 5th finger. This condition in turn retards the filling-in of the bone-forming cells. As a result of this series of delays, the radial side of this phalanx is left shorter than normal, thus producing a visible slanting of its upper surface. The ulnar side is also shorter but not as much as the radial side. Consequently, the middle phalanx is shorter than normal and justifies Bell's inclusion of clinodactyly among the various forms of brachydactyly.

SUMMARY

Hereditary "crooked little fingers" have been classified into three groups based on internal causes rather than on outward appearance; (1) *incomplete ossification;* (2) *short tendon;* (3) *fused ossification.* Clinodactyly belongs to the first group.

It is a minor digital anomaly in which the middle phalanx is shorter than normal, but distinctly shorter on the radial than on the ulnar side, with the result that the terminal phalanx of the 5th finger inclines radially somewhere between 15° to 30°. There is no curvature in the direction of flexion. An analysis by inspection of pedigrees and a numerical test on the pooled data from 51 sibships lead to the conclusion that clinodactyly is an autosomal dominant. There is a slight lack of penetrance; in 4 of the sibships neither parent was affected. An X-ray study of several cases, along with Mall's observations on ossification centers in human embryos, and discussed in the light of our knowledge of the histogenesis of cartilage and bone, leads to the conclusion that clinodactyly is the result of a developmental arrest caused either by a delay of the ossification process or by a delay in the transformation phases of the cartilage cells. The best estimate at present of its incidence in the population is about 1 in 1000.

REFERENCES

Bell, J. 1951. On Hereditary Digital Anomalies. Part 1, On Brachydactyly and Symphalangism. *The Treasury of Human Inheritance,* 5: 1–31.

Buschke, F. 1935. The radiological examination of the skeleton of triplets. *J. Hered.* 26: 391–409.

Cockayne, E. A. 1933. *Inherited abnormalities of the skin and its appendages.* Oxford University Press. pp. 394.

Greulich, W. W. and Pyle, S. Idell. 1950. *Radiographic atlas of skeletal development of the hand and wrist.* Stanford: Stanford University Press. pp. 190.

Hefner, R. A. 1924. Inherited Abnormalities of the Fingers. Subterminal Articulation in the Proximal Joint of the Little Finger. *J. Hered.* 15: 323–9.

Hefner, R. A. 1929. Inheritance of Crooked Little Fingers (Streblomicrodactyly). J. Hered. 20: 395–398.

Hefner, R. A. 1941. Crooked Little Fingers. *J. Hered.* 32: 37–38.

HOGBEN, L. 1946. *An Introduction to Mathematical Genetics.* New York: W. W. Norton and Company.

KOENNER, D. M. 1924. Abnormalities of the Fingers. *J. Hered.*, 15: 323–329.

MALL, F. P. 1906. On Ossification Centers in Human Embryos Less Than One Hundred Days Old. *Am. J. Anat.*, 5: 433–458.

MOORE, W. G., & MESSINA, P. 1936. Camptodactylism in Its Variable Expression. *J. Hered.* 27: 27–30.

MULLER, H. J. 1949. Redintegration of the Symposium on Genetics, paleontology and evolution. Chapter 23. *Genetics, Paleontology, and Evolution* (editors G. L. Jepsen, Ernest Mayr, and G. G. Simpson) Princeton: Princeton Univ. Press.

POL, DR. 1921. Brachydaktylie-Klinodaktylie-Hyperphalangie und ihre Grundlagen: Form und Entstehung der meist unter dem Bild der Brachydaktylie auftretenden Varietaten. Anomalien und Missibildungen der Hand und des Fusses. *Virchow's Arch. f. Path. Anat.*, 229: 388–530.

SPENCER, WARREN P. 1949. Gene homologies and the mutants of Drosophila hydei. Chapter 3, *Genetics, Paleontology and Evolution* (editors, G. L. Jepsen, Ernest Mayr, and G. G. Simpson) Princeton: Princeton University Press.

STECHER, ROBERT M. 1940. Heberden's nodes: the incidence of hypertropic arthritis of the fingers. *New England J. Med.*, 222: 300–308.

STODDARD, S. E. 1939. Nomenclature of Hereditary Crooked Fingers. *J. Hered.*, 30: 511–512.

STREETER, GEORGE L. 1949. *Developmental Horizons in Human Embryos:* A Review of the Histogenesis of Cartilage and Bone. Carnegie Institution of Washington, Publication 583: 149–167.

Some General Properties of Recessive Inheritance

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INTRODUCTION

IN VIEW of the increasing interest of research in human genetics in recent years, it seems desirable to point out some general properties of the well-known Synder's method of analyzing familial data with autosomal dominance and at the same time discuss some of the closely related problems. In accordance with usual notations, we use p to denote the frequency of the dominant allele (A) and q that of the recessive (a) of a gene-pair in a population where $p + q = 1$. Snyder (1934) showed that in a large random-mating population the proportion of recessive offspring among the various types of phenotypic parental matings is

one parent dominant: $$S_1 = \frac{q}{1+q} < \tfrac{1}{2} \tag{1}$$

both parents dominant: $$S_2 = \frac{q^2}{(1+q)^2} < \tfrac{1}{4} \tag{2}$$

where the subscript of S indicates the number of dominant parents involved in the mating. Note that S_2 is the square of S_1.

With dominance and thus only two distinguishable phenotypes, the Hardy-Weinberg distribution of genotypes in the general population cannot be directly observed but it may be recovered in an indirect manner. If we have a number of random recessive individuals and trace their parental phenotypes, we will find that the three types of parental phenotypic combinations in simple binomial proportions:

Parental phenotypes	Dom. × Dom.	Dom. × Rec.	Rec. × Rec.
Proportion among matings producing *aa* offspring	p^2	$2pq$	q^2

(3)

In the case of one pair of genes, this *conditional* distribution of parental phenotypes of recessive individuals in a panmictic population is the same as the Hardy-Weinberg distribution of genotypes in the population. Although the proportions (3) may be obtained from a table of random matings with their corresponding offspring, it is useful for our later generalizations to deduce it from the following consideration. Since the matings produce recessive(s), each parent must have at least one recessive gene; i.e. the mating must be of the type $Xa \times Xa$ where X stands for the unspecified gene. Since the frequency of the gene A is p in the general population, the probability that both X should be A is p^2, assuming random mating. Similarly,

Received February 16, 1953.

the probability that both X be a is q^2 and that one X is A and the other a is $2pq$.

We shall show in the following that (1), (2) and (3) are true for all multiple recessive traits whatever the number of pairs of genes involved.

Multiple Recessiveness

In order to illustrate the point at issue we shall examine the case of double-recessiveness (due to two pairs of homozygous recessive genes) more in detail before we pass to generalizations. Let p_1, q_1 be the frequencies of the A-a pair and p_2, q_2 be those of the B-b pair where $p_i + q_i = 1$. We assume that only the genotype *aabb* shows the recessive trait while the other eight genotypes are all dominants and alike in phenotype. In such cases the A, a and B, b are sometimes called "duplicate" genes. In a panmictic population the proportions of dominants and recessives are $1 - q_1^2q_2^2$ and $q_1^2q_2^2$, respectively.

With nine genotypes there are $(9 \times 10)/2 = 45$ different genotypic matings, not distinguishing reciprocals, as we are dealing with autosomal genes. Since there are eight dominant genotypes there will be $(8 \times 9)/2 = 36$ different genotypic matings of the type Dom. $\times$ Dom., 8 of the type Dom. $\times$ Rec. and only one of

TABLE 1. FREQUENCIES OF PHENOTYPIC MATINGS AND THEIR RECESSIVE OFFSPRING FOR TWO PAIRS OF DUPLICATE GENES

NO. OF GENOTYPIC MATINGS	PARENTAL PHENOTYPES	MATING FREQUENCY IN GENERAL POPULATION	PROPORTION OF RECESSIVE OFFSPRING IN GENERAL POPULATION
36	Dom. $\times$ Dom.	$(1 - q_1^2q_2^2)^2$	$q_1^2q_2^2(1 - q_1q_2)^2$
8	Dom. $\times$ Rec.	$2(1 - q_1^2q_2^2)q_1^2q_2^2$	$2q_1^3q_2^3(1 - q_1q_2)$
1	Rec. $\times$ Rec.	$(q_1^2q_2^2)^2$	$q_1^4q_2^4$
45	All	1.00	$q_1^2q_2^2$

the type Rec. $\times$ Rec. The frequencies of the three types of phenotypic parental combinations in the general population together with their total output of recessive offspring are given in Table 1.

The mating frequencies listed in Table 1 need no comment. The proportions of recessives given in its last column are obtained as follows. Of the 8 matings with one dominant parent, only three of them produce recessive offspring. This is easily seen to be the case by considering the fact that such a dominant parent must have at least one dominant gene and at the same time at least one recessive gene of each pair. Therefore, the dominant parent could only be one of the three genotypes: *AaBb*, *Aabb* or *aaBb* if they produce any recessives. Of the 36 Dom. $\times$ Dom. matings, only $(3 \times 4)/2 = 6$ of them produce recessive offspring because such matings involve only parents of the three genotypes just indicated. These recessive-producing matings have been tabulated with their corresponding frequencies and segregation ratios by Hogben (1932) for panmictic populations and recently again by Steinberg, *et al.* (1952). It is easy to verify that the proportions given in the last column of Table 1 are those of the recessives produced by the 6 Dom. $\times$ Dom. and 3 Dom. $\times$ Rec. matings where the dominant parent is *AaBb*, *Aabb* or *aaBb*.

The important feature of Table 1 is, however, that it is of the same form as what would be obtained for just one pair of genes with dominance except replacing q_1q_2 by q. Thus, Snyder's method gives:

$$\text{one parent dominant:} \quad S_1 = \frac{q_1 q_2}{1 + q_1 q_2} \tag{1'}$$

$$\text{both parents dominant:} \quad S_2 = \frac{(q_1 q_2)^2}{(1 + q_1 q_2)^2} \tag{2'}$$

Further, the last column of Table 1 also shows that the phenotypic parental combinations of recessive children are, like the case of single pair of genes, in simple binomial proportions:

$$\begin{array}{lll} \text{Dom.} \times \text{Dom.} & \text{Dom.} \times \text{Rec.} & \text{Rec.} \times \text{Rec.} \\ (1 - q_1q_1)^2, & 2(1 - q_1q_2)q_1q_2\,, & (q_1q_2)^2 \end{array} \tag{3'}$$

Briefly, the results (1'), (2') and (3') for two pairs of duplicate genes are the same as (1), (2) and (3) for just one pair of genes, except replacing q_1q_2 by q.

In order to reach generalizations we may examine the situation from a different view-point. The similarity between the two sets of results becomes immediately self-evident from the consideration that only *ab*-gametes with a frequency q_1q_2 in the general population are "recessive" while the other three kinds of gametes carry at least one dominant gene with a pooled frequency $1 - q_1q_2$. With random union of the four kinds of gametes (which implies the random union of the "dominant" and "recessive" gametes), it is clear that the total phenotypic results of *all* matings in the population are the same as those of one pair of genes with q recessive gametes and $1 - q$ dominant gametes. This consideration permits an immediate generalization to the case of recessiveness due to k pairs of homozygous genes. Then, the recessive genotype is *aabbcc* $\cdots$ and the frequency of the recessive gametes (*abc* $\cdots$) is $q_1 \cdots q_k$ while the pooled frequency of gametes carrying at least one dominant gene is $1 - q_1 \cdots q_k$. But, there are still only three phenotypic types of mating in the general population whose total recessive offspring is $(q_1 \cdots q_k)^2$. Therefore, the relations (1), (2) and (3) still hold except that q is to be interpreted as the frequency of recessive *gametes*, rather than that of a single recessive allele. In view of this property, we may call those three expressions "the general law of recessive inheritance", applicable to k-fold recessive traits where one dominant gene (it does not matter which) overrides any number of recessive genes in a genotype. It follows that an agreement with (1), (2) and (3) of an observed set of data does not tell us whether the recessive trait is due to one, two or more pairs of genes. All we know is that it is a pure recessive.

The relation (3') has also been pointed out by Steinberg, *et al.* (1952) but that they use it to justify their specific double-recessive hypothesis of psoriasis loses some of its strength in view of the above discussions. Their further assumption that the two pairs of genes are of equal frequency (in order to fit their observed results) is entirely arbitrary.

Perhaps it should be remarked that a k-fold recessive condition does not imply

its rareness in the general population. It could well be a common trait. Only the segregation ratio among certain types of genotypic mating is low.

Segregating Families

Another type of inquiry into the inheritance of recessive traits is to concentrate on the segregating families only. We shall use R to designate the proportion of recessives among the offspring of such families. Thus, for one pair of genes, the only segregating family of the Dom. × Rec. type is $Aa \times aa$, and that of the Dom. × Dom. type is $Aa \times Aa$. Hence, we have, respectively,

$$R_1 = \tfrac{1}{2}, \qquad R_2 = \tfrac{1}{4} \tag{4}$$

where the subscript indicates the number of dominant parents in the family. In this simple case the values of R_1 and R_2 are independent of the gene frequencies in the general population. But the relation $R_2 = R_1^2$ gains a new significance in view of the subsequent generalizations. All the proportions given in this section are their true values. The effect of bias in observed data will be briefly discussed in the next section.

Now, let us turn to the case of double recessiveness. The proportion of recessive offspring among the three segregating Dom. × Rec. matings (mentioned in the previous section) may be easily calculated:

$$R_1 = \tfrac{1}{2} - \underset{\text{(Hogben)}}{\frac{p_1 p_2}{2(p_1 + q_2)}} = \underset{\text{(Steinberg, } et.\ al\text{)}}{\frac{1 - q_1 q_2}{2(p_1 + p_2)}} = \underset{\text{(Li)}}{\frac{1 - q_1 q_2}{(2 - q_1)(2 - q_2) - q_1 q_2}} \tag{5}$$

It is the weighted average of the Mendelian recessive proportions ¼, ½ and ½ of the three segregating Dom. × Rec. families, the weights being the relative frequencies of the three genotypic unions. Therefore, its value lies between ¼ and ½, depending upon the gene frequencies (Figs. 1, 2, 3). The last form of (5) given by the present author, though not the simplest for the case of two pairs of genes, permits immediate generalization to the case of k-fold recessiveness, as will be shown later in the section.

The proportion of recessive offspring among the six segregating Dom. × Dom. families is obtained in a similar manner:

$$R_2 = \tfrac{1}{4} - \underset{\text{(Hogben)}}{\frac{p_1 p_2(2p_1 + 2p_2 - p_1 p_2)}{4(p_1 + p_2)^2}} = \underset{\text{(Steinberg, } et\ al.\text{)}}{\frac{(1 - q_1 q_2)^2}{4(p_1 + p_2)^2}} = \underset{\text{(Li)}}{R_1^2} \tag{6}$$

It is the weighted average of the recessive proportions 1/16, 1/8, 1/8, ¼, ¼, ¼ of the six segregating genotypic unions. Its value lies between 1/16 and ¼ (Figs. 2 and 3). The relation $R_2 = R_1^2$, whatever the gene frequencies, seemed to have escaped the attention of Hogben (1932) but is brought out clearly by Steinberg's expressions (1952). However, they did not use this relation directly to test their double-recessive hypothesis of psoriasis, and, instead, used the ratio $R_1/R_2 = 1/R_1$. The advantage of doing this is not clear.

For the general case of k-fold recessiveness there will be $2^k - 1$ segregating geno-

typic matings out of the $3^k - 1$ matings of the type Dom. × Rec. Thus, for $k = 3$, there are 7 segregating matings (out of 26) involving one dominant parent, as enumerated in Table 2.

The average proportion of recessives for the seven segregating families of Table 2 may be readily found. Taking the common factor $q_1q_2q_3$ out of the terms in column f, we see the sum of the rest is simply $(2p_1 + q_1)(2p_2 + q_2)(2p_3 + q_3) - q_1q_2q_3$.

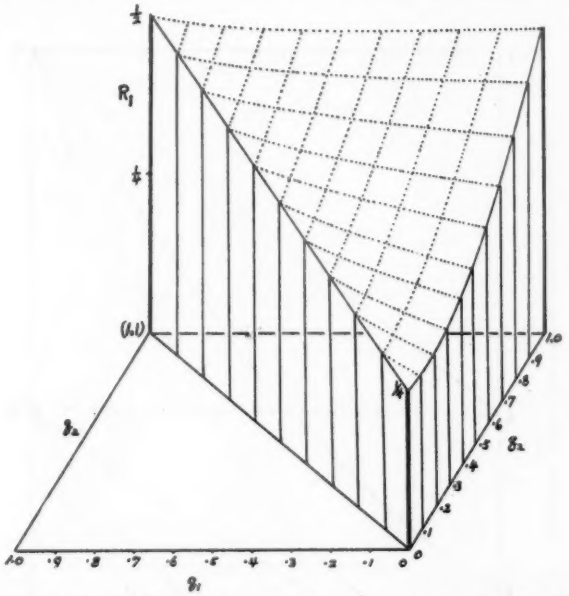

FIG. 1. Values of R_1 (vertical axis) for various values of q_1 and q_2 as given by formula (5). Only the upper right half of the surface is shown in the figure as the other half is symmetrical to it. The intersection of the R_1 surface and the $q_1 = q_2$ plane is a straight line (also see Fig. 2). Note that R_1 is close to ½ when one recessive gene has a very high frequency (near unity) whatever the frequencies of the other pair. In general, when the frequencies of $k-1$ recessive genes are very high, the value of R_1 will be near to ½, reducing approximately to the case of simple recessiveness.

Forming a new column fr and again ignoring its common factor $q_1q_2q_3$, we find its sum to be $(p_1 + q_1)(p_2 + q_2)(p_3 + q_3) - q_1q_2q_3$. Hence,

$$R_1 = \frac{\sum fr}{\sum f} = \frac{1 - q_1q_2q_3}{(2 - q_1)(2 - q_2)(2 - q_3) - q_1q_2q_3} \qquad (5')$$

Its value lies between ⅛ and ½ (Figs. 2 and 3). An examination of the construction of Table 2 shows that its algebraic scheme would be of the same form if we have four or more pairs of genes. The generalization of (5′) to k-fold recessives is obvious. Note that the general form covers the extreme case of $k = 1$ as well. Then, it reduces to $(1 - q_1)/(2 - 2q_1) = ½$, as noted before.

Incidentally, if we divide the total frequency of recessive offspring of Table 2

(including all common factors so that the proportion is on a populational basis) by the total frequency of *all* Dom. × Rec. matings in the population, we would obtain a direct verification of the generalized form of (1), viz., $S_1 = q_1q_2q_3/(1 + q_1q_2q_3)$.

As to finding the average proportion of recessive offspring among the segregating matings with both parents dominant, it is tedious to enumerate the $(7 \times 8)/2 = 28$ possible genotypic unions (out of 351) that can produce recessives. Fortunately,

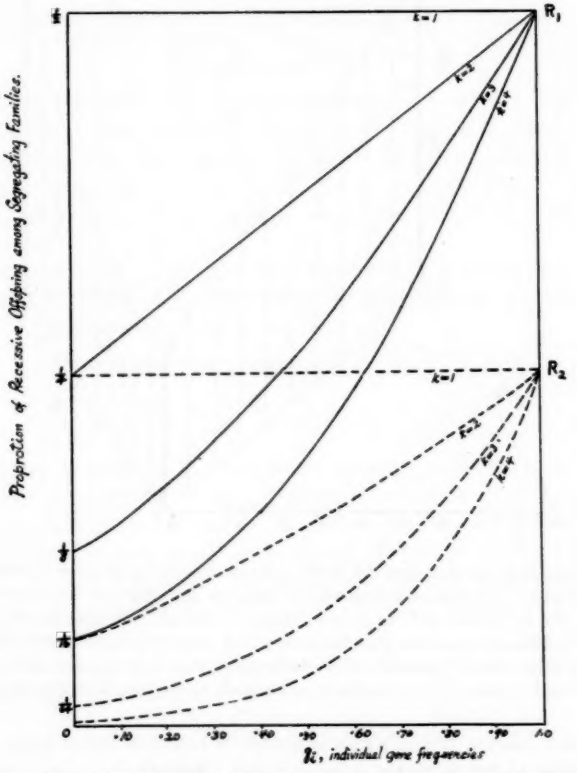

FIG. 2. Values of R_1 and R_2 for k (=1, 2, 3, 4) pairs of genes with equal frequencies ($q_1 = q_2 = q_3 = q_4$).

its undertaking becomes wholly unnecessary by considering the following general principle. The 28 segregating Dom. × Dom. matings involve only those dominants that have at least one dominant gene and at least one recessive allele of each gene-pair. In other words, all of these dominant parents belong to the seven genotypes listed in Table 2. Moreover, these 28 matings constitute a random-mating sub-population by themselves. Then, note that $\sum fr$ is the total recessive gametic output from the 7 dominant genotypes whose total frequency is $\sum f$. Therefore, on

random mating, there will be $[\sum fr]^2$ recessive offspring relative to a total mating frequency $[\sum f]^2$. Hence,

$$R_2 = \frac{[\sum fr]^2}{[\sum f]^2} = R_1^2 \tag{6'}$$

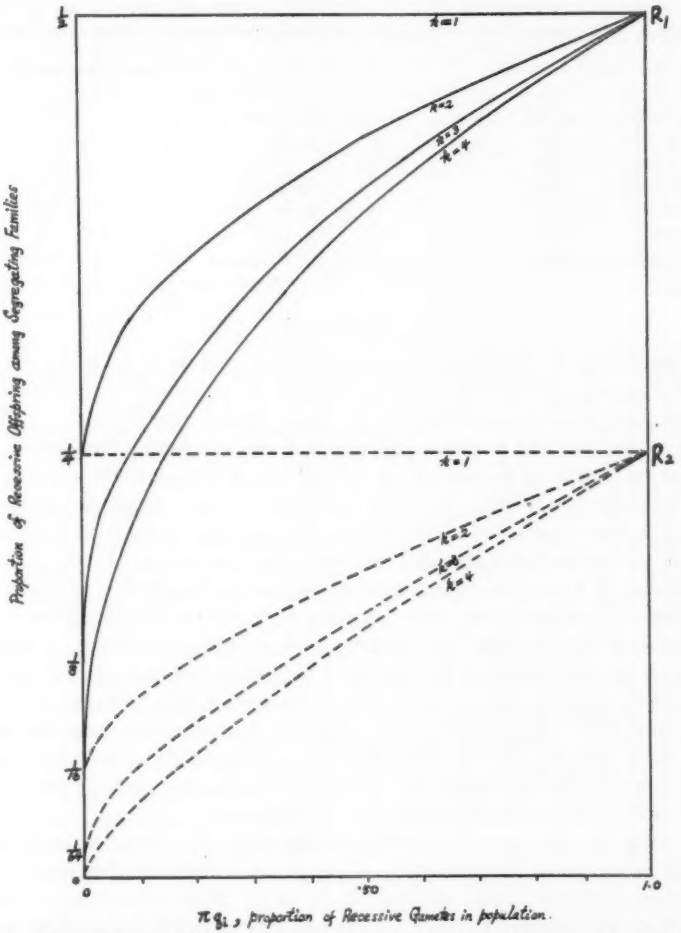

FIG. 3. Values of R_1 and R_2 for given proportions of the pure recessive gametes in the general population, assuming that there are k pairs of genes with equal frequencies.

Its value lies between $1/64$ and $1/4$ (Figs. 2 and 3). Obviously, the same argument applies to any number of duplicate genes, and the relation (6') is perfectly general.

It should be noted that the above argument applies equally well to the proportions S's investigated in the previous section. The only difference between the

S's and R's is that the latter refers to a smaller subpopulation of which the segregation ratio r of each mating is not zero while the former refers to a larger random-mating subpopulation including all crosses with $r = 0$. A moment's reflection on their analogy shows that "the law of squares" still holds; viz., $S_2 = S_1^2$.

TABLE 2. SEGREGATING FAMILIES WITH ONE DOMINANT PARENT FOR THREE PAIRS OF DUPLICATE GENES. THE COMMON FACTOR $2(q_1q_2q_3)^2$ HAS BEEN OMITTED IN COLUMN f FOR BREVITY

DOM. × REC. PARENTAL GENOTYPES	FREQUENCY OF MATING f	RECESSIVE SEGREGATION RATIO r
$AaBbCc \times aabbcc$	$2p_1q_1 \cdot 2p_2q_2 \cdot 2p_3q_3$	1/8
$AaBbcc \times aabbcc$	$2p_1q_1 \cdot 2p_2q_2 \cdot q_3^2$	1/4
$AabbCc \times aabbcc$	$2p_1q_1 \cdot q_2^2 \cdot 2p_3q_3$	1/4
$aaBbCc \times aabbcc$	$q_1^2 \cdot 2p_2q_2 \cdot 2p_3q_3$	1/4
$Aabbcc \times aabbcc$	$2p_1q_1 \cdot q_2^2 \cdot q_3^2$	1/2
$aaBbcc \times aabbcc$	$q_1^2 \cdot 2p_2q_2 \cdot q_3^2$	1/2
$aabbCc \times aabbcc$	$q_1^2 \cdot q_2^2 \cdot 2p_3q_3$	1/2

DISCUSSION

The proportion of recessives among segregating families as given by R_1 and R_2 in the last section are their true values. For any set of collected data, however, the observed proportion of recessives will be higher than its corresponding true value because of the fact that a certain proportion of the segregating families will fail to segregate by chance on account of the limited size of human sibships and will thus not be included in the data. This bias is systematic and cannot be overcome by collecting a large number of small sibships. For one pair of genes with dominance, there are various methods available to correct this bias created by the omission of such families. It is not the intention of the author to discuss the methods of correction here. It suffices to say that they vary with the way by which the recessive probands were first brought into record. The statistical procedure of correcting the bias for one pair of factors is based upon the unique fact that whether the segregating family involves one or two dominant parents their genotypic constitution will be completely determined by the presence of at least one recessive member among their offspring. Hence the probability of producing a recessive offspring remains constant for all families of a given phenotypic type and the proportion of families that failed to segregate may thus be estimated.

But, this is not the case with multiple recessiveness. For instance, in the case of double-recessive traits, the probability of producing a recessive offspring of a segregating Dom. × Dom. family may be 1/16, 1/8 or 1/4. When we encounter a sibship with at least one recessive member, we have no way of telling to which of the three categories of genotypic unions this sibship belongs. There are at present no methods known to the writer to correct the crude proportion of recessives when differential probabilities are involved. It might be possible to employ the average value of these probabilities as a basis for correction in an iteration process, but no investigation along this line has been made yet. This shows the practical difficulty of arriving at true values of R_1 and R_2 for multiple recessiveness.

In this connection it should be noticed that Steinberg, *et al.*, suggesting a double

recessive hypothesis of psoriasis on one hand, applied one of the monofactor correction methods on the other (1951, p. 273). The crude proportion of psoriasis offspring with two normal (dominant by hypothesis) parents is 449/2039 = 22% according to their Table 6. The correction they adopted is (449 − 409)/(2039 − 409) = 40/1630 = 2.45%. This correction method is valid for one pair of genes *and* when the probability of ascertaining a sibship is directly proportional to the number of recessive members in that sibship (Haldane, 1938). Other methods of correction would give a higher proportion of psoriasis, although lower than 22%. But, anyway, since their values of R_1 and R_2 are so much lower than $\frac{1}{2}$ and $\frac{1}{4}$, respectively, it seems justified in concluding that psoriasis could not be a simple recessive trait.

The proportions of recessive offspring among *all* matings of given parental phenotypes (Snyder's ratio S_1 and S_2) need no correction for the size of sibship because the possible segregating families that failed to do so are automatically included in the data anyway.

Naturally the question arises as to how to distinguish between a simple and a multiple recessive condition from the kind of data such as we have in human genetics. Relations (1), (2) and (3) are true for all cases (taking $q = q_1 \cdots q_k$) and obviously of no help. One clue is that when the proportions of recessives among segregating families (which may be corrected somehow as a trial value) are significantly lower than $\frac{1}{2}$ and $\frac{1}{4}$ for families with one and two dominant parents, respectively, we would have reason to suspect the possibility that the trait is a multiple recessive condition. Further, if they are significantly lower than $\frac{1}{4}$ and $\frac{1}{16}$, respectively, it would suggest that at least three pairs of recessive genes are involved, and so on. In general, for k-fold recessiveness, the value of R_1 is between $\frac{1}{2}$ and $\frac{1}{2^k}$; and that of R_2 between $\frac{1}{4}$ and $\frac{1}{4^k}$. When all the q's are small (rare recessive trait), R_1 and R_2 would be near to their minimum values. On the other hand, if the q's are large (near unity), R_1 and R_2 would not be much lower than $\frac{1}{2}$ and $\frac{1}{4}$, respectively, no matter how many pairs of genes are involved. Thus, we see the difficulty that we cannot always use the minimum values of R_1 and R_2 to determine the number of genes involved. Even for $k = 3$ or 4 with moderate values of the q's, the proportions R_1 and R_2 can assume such a wide range of values that they are of little practical value to help determine the number of genes involved, not to mention estimating the separate values of q_i. There is apparently no clear-cut way of determining the exact number of genes involved in a multiple recessive condition from the human family data.

In the particular case of psoriasis mentioned above, if we take $R_1 = .090$ and $R_2 = .0245$ (although they do not conform with the law of squares) as reported, we see that they happen to be so much lower than their minimum theoretical values (.2500 and .0625) for double recessiveness that a triple recessiveness would seem a more plausible guess. In fact, the number of recessive genes may be any number greater than three.

SUMMARY

Some of the general properties of the inheritance of multiple recessive traits have been investigated. As a result, some of the well-known formulas for one or two pairs

of genes have been generalized to cover the case involving any number (k) of pairs of loci. In the following, q_i ($i = 1, 2, \cdots, k$) stands for the frequency of the recessive allele of a gene-pair and $\Pi q_i = q_1 q_2 \cdots q_k$ is the frequency of the pure recessive gametes in the general population. All of the following results refer to a large random mating population.

(1) The first generalization concerns the proportion of recessive offspring among *all* matings with one dominant parent:

$$S_1 = \frac{\Pi q_i}{1 + \Pi q_i}; \qquad 0 < S_1 < \tfrac{1}{2}$$

It is the generalized Snyder's "populational ratios" for one pair of genes.

(2) The second generalization concerns the proportion of recessive offspring among the *segregating* matings with one dominant parent:

$$R_1 = \frac{1 - \Pi q_i}{\Pi(2 - q_i) - \Pi q_i}; \qquad \tfrac{1}{2} < R_1 < (\tfrac{1}{2})^k$$

It is the generalized Hogben's "segregation ratios" for two pairs of duplicate genes.

(3) The third generalization may be termed "the law of squares", *i.e.* the corresponding proportions of recessives for the above two cases when *both* parents are dominant are

$$R_2 = R_1^2; \qquad S_2 = S_1^2$$

whatever the number of pairs of genes and whatever their frequencies.

(4) The fourth generalization is that the frequencies of parental phenotypes of a given random group of multiple recessive individuals are in simple binomial proportions:

Dom. × Dom.	Dom. × Rec.	Rec. × Rec.
$(1 - \Pi q_i)^2$	$2(1 - \Pi q_i)\Pi q_i$	$(\Pi q_i)^2$

(5) Some of the difficulties to arrive at the true values of R_1 and R_2 from human data have been discussed. The difficulties and possibilities of distinguishing between the various degrees of recessiveness have also been indicated. There seems no clear cut method of determining the exact number of recessive genes involved except in the simplest case of unit character.

ACKNOWLEDGMENTS

The writer wishes to thank Prof. Bentley Glass in suggesting this problem for investigation. He also wishes to express his gratitude to Prof. Laurence H. Snyder for his generous help in the preparation of this manuscript.

REFERENCES

HALDANE, J. B. S. 1938. The estimation of the frequencies of recessive conditions in man. *Ann. Eugen.* 8: 255–262.

HOGBEN, L. 1932. The genetical analysis of familial traits. II. Double gene substitutions, with special reference to hereditary dwarfism. *J. Genet.* 25: 211–240.

SNYDER, L. H. 1934. Studies in human inheritance. X. A table to determine the proportion of recessives to be expected in various matings involving a unit character. *Genetics* 19: 1–17.

STEINBERG, A. G.; BECKER, S. W.; FITZPATRICK, T. B. & KIERLAND, R. R. 1951. A genetical and statistical study of psoriasis. *Am. J. Human Genet.* 3: 267–281.

—, —, —, & —. 1952. A further note on the genetics of psoriasis. *Am. J. Human Genet.* 4: 373–375.

BOOK REVIEWS

General Physiology

By BRADLEY T. SCHEER (University of Oregon) New York: John Wiley and Sons, Inc. 1953. Pp. 613; 110 figs., 28 tables. $7.00.

A NEW physiology textbook with some evidence of a new point of view. The book is divided into five major sections; (1) The Physicochemical Foundation of Life, (2) The Chemical Dynamics of Life, (3) Energy Transformation in Cells and Organisms, (4) The Development of Organisms and (5) The Integration of the Organism.

The first section is a very good presentation of basic physicochemical concepts. The last chapter of this section on the physicochemical structure of cells is brief, but it is sufficiently inclusive to bring into focus some of the newer findings relative to DNA and hereditary materials of the cell. Sections two and three appear to be up-to-date considerations of metabolic processes. The last chapter of section three is entitled: Physiological Aspects of Radiant Energy. While this chapter presents a good general discussion of radiation the geneticist will find very little pertaining to the production of genic or chromosomic mutations.

It is section four which to this reviewer presents the most refreshing and hopeful sign. Here one finds a physiology textbook actually considering, to some extent at least, physiological processes in terms of what genes may do. Is it possible that physiologists may some day come out of their castles and enjoy with others the world as a whole? Even a topic such as the integration of the organism has found its way into a physiology textbook and fortunately it appears in not too ancient a garb.

A bibliography of 1453 titles with many of the references dated as late as 1952 is, in and of itself, evidence of the modernity of the book.

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Genetics and Disease

By TAGE KEMP, M.D., (Professor of Human Genetics, University of Copenhagen). Copenhagen: Ejnar Munksgaard, 1951. Pp. 330, 100 figs.

IN 1948 your reviewer had the great pleasure of visiting Professor Kemp at his laboratory in Copenhagen. Subsequent tourist shopping included the purchase of the 1943 edition of his text which was then available only in Danish. This Danish edition was expanded somewhat and then translated into English by Elizabeth Aagesen. The result was "Genetics and Disease" published for the first time in English in 1951. Essentially this book is the 1943 Danish edition brought up to date but with rather minor revisions. Chapter headings, form and general organization are practically identical with the original edition. Such revisions as were made are stated to be due to James Andrews of London.

The Danish edition states that the book is for students and physicians. Presumably the same applies to the English version though no statement in this regard is to be found in the latter. It is quite clear that it is written for those who have had no previous contact with genetics. Professor Kemp's students in the Medical School are fortunate in that they get exposed to the general concepts of human genetics, while in this country the majority of physicians commence their practice in complete ignorance of this science. "Genetics and

Disease" is one of the very few texts which can provide the medical student, who is without previous training in genetics, with what he expects in a short text. The student for whom this book is designed is anxious to get to the practice of medical genetics with as little attention to the principles as possible.

The book is divided into five parts and it is logical that the student be encouraged to consider the principles before proceeding to his main interests. Part one is an explanation of the basis of heredity as demonstrated primarily by Drosophila and the other experimental organisms. As a whole there is nothing particularly fancy in this section. A few unique features worth copying by future authors might be mentioned. Figures 9 and 10 make clear the difference in the way a pedigree of dominant inheritance looks compared with a pedigree of a recessive character. It is important for the beginning student to be able to visualize this difference and it is usually difficult for him to do so. The adaptation of the material originally presented by Neel, Kodani, Brewer and Anderson on consanguinity in Japanese and European populations is illuminating. It is not easy to present the principles of genetics and cytology in 90 pages, as Professor Kemp has done. It is unlikely that our average physician is acquainted with all of the material presented. It is to be hoped that the day will come when Part one will be too elementary for him.

Part two is a description of the methods of medical genetics. The techniques introduced here are the tools needed in determining the extent and type of hereditary basis for a particular disease. This section presents the theory and methods of practical interest to the medical student and physician. Coverage of the essentials is very good but there is one point which the reviewer would liked to have seen expanded. The description of Weinberg's methods for testing data for the dominant or recessive type of inheritance is clear but it might have been valuable to add an example for a specific disease where the expected expression of the characteristic was worked out step-by-step and compared with the observed. The reviewer recommends the Macklin method of calculation of the percentage of affected children expected, as it can be compared directly with the total percentage of affected children observed. Such a procedure makes good sense to the physician or medical research person, and would encourage him to try the method himself.

Part three is concerned with "normal" heredity, whatever that may be. In this book it includes a range of subjects from anthropology to the prevention of erythroblastosis. Chapter 20 is on blood groups. It is not only up-to-date and complete but is also an excellent example of clear exposition of a highly complicated subject. The next chapter on psychic traits is only three pages long and could just as well have been omitted. It is difficult to imagine a more important subject than the relationship between heredity and intelligence and, though it seems to be of less interest to the physician than are the blood groups, it deserves serious attention.

Part four is a descriptive catalog, nicely illustrated, of some of the more gruesome diseases with an hereditary basis. This is the part which the physician has been waiting for and probably would read first. There seems to have been a very good selection of the material to be included. While this is the longest section of the book it seems to present the least opportunities for suggestions for improvements. It is well done.

Part five is entitled "Genetic Hygiene." This corresponds to what might be called negative eugenics. It differs mainly in that the goal is to benefit the individual or his family primarily, and then society as a whole, by limiting his reproduction. The use of the word "hygiene" is to emphasize that it is a medical subject with its main task that of preventing disease. The patient himself must apply for the privilege of sterilization or induced abortion. Careful precautions are taken to guarantee that the request is in actuality a voluntary one on the part of the patient. Because the program is both voluntary and beneficial from the

patient's point of view, it has expanded very rapidly in the two decades since its inception. Sterilizations increased from 108 for the years 1929–34 to 2,332 for 1946–50. A much more remarkable phenomenon followed the passage in 1939 of a law permitting induced abortion on eugenic grounds. In the ten year period thereafter, 19,506 persons availed themselves of this opportunity. It would seem obvious that women prefer to terminate a pregnancy rather than terminate their fertility. The above figures are for Denmark but a comparable experience has been reported for Iceland, Sweden and Finland.

It is certainly doubtful whether even this large program has changed the genotype of the whole Danish people very much as yet, though, if continued, it would do so eventually. The immediate benefits are for the families concerned and are of a socio-economic nature. A follow-up study of the participants in this program as the years pass could not help but yield most interesting data regarding future adjustments and results of the experimentation with their reproductive capacities. This is the shortest, but by far the most interesting, section of the book.

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ANNUAL MEETING THE AMERICAN SOCIETY OF HUMAN GENETICS

SINCE the IX International Congress of Genetics is scheduled for Bellagio, Italy, August 24–31, THE AMERICAN SOCIETY OF HUMAN GENETICS will not hold its annual meeting during the month of September as it has done the past three years, but will meet at Boston, Mass., December 28–30, under the auspices of the A.A.A.S. The Sheraton Plaza (formerly the Copley Plaza) will be the headquarters of The American Society of Human Genetics, The Genetics Society of America and The American Society of Naturalists. If you plan to attend the Boston meeting don't fail to reserve your room early. The full program is not prepared as yet, but a preliminary one is ready and is presented below.

PRELIMINARY PROGRAM

Sunday, Dec. 27.

Evening: Meeting of the Board of Directors

Monday, Dec. 28

Morning: Short papers
Afternoon: Symposium: "*Human Genetics and Medical Education*"
Afternoon 4:30: Annual Business Meeting

Tuesday, Dec. 29

Morning: Short papers
Afternoon: Symposium: "*Genetic Factors Affecting Intelligence.*" (Sponsored jointly with The American Eugenics Society)
Evening 6 P.M.: Annual Dinner and Address by President C. P. Oliver at the Copley Square Hotel.

Wednesday, Dec. 30

Morning: Short papers
Afternoon: Symposium: "*Genetics and the Races of Man.*" (Sponsored jointly with The Genetics Society of America)

The program committee is convinced that the above symposia will be exceptionally interesting. They represent our first major attempt to correlate our interests with those of other societies. Why not help to make these meetings successful by attending them. If you wish the Society to develop along the lines you think are correct, don't fail to attend the annual business meeting and to present your ideas there. If any reader who is not a member of the Society wishes to become one he should write to the secretary for details.

SHELDON C. REED
Secretary

BIBLIOGRAPHY OF HUMAN GENETICS

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THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made, and is being made to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or any current reference which it seems probable may be missed as a result of its appearance in a journal which probably is not systematically covered by the bibliographic editor. If a reference to an article is sent in be sure that it is complete with respect to name of author(s), year of publication, title of article, name of journal, volume number, and first and last page numbers. If the reference is to a book be sure that it includes name of author(s), year of publication, title, name of publisher, place of publication, and number of pages.

ALDER, A., & SCHAUB, F. 1952. Gleichzeitiges Vorkommen von Pelgerscher Kernanomalie und von Blutkrankheiten. [Association of Pelger's nuclear abnormality with blood dyscrasias.] *Deut. med. Wschr.* 77(42): 1290–1293.

ALDER, E. 1952. Familial cerebral palsy. *Mschr. Psychiat.*, Basel 124(1): 7–21.

ANONYMOUS. 1952. Anticipation in inheritance of diabetes. *J. Am. M. Ass.* 150(8): 796–798.

ANONYMOUS. 1952. Blood grouping tests; not admissible as proof of paternity. *J. Am. M. Ass.* 150(6): 611.

ANONYMOUS. 1952. Prenatal sex test. *What's New* 170: 4–6.

APPEL, L., & VAN BOGAERT, L. 1952. Etudes sur la paraplégie spasmodique familiale. IV. La famille Fev. . .: forme trés tardive; contribution histopathologique. [Spasmodic familial paraplegia. IV. The Fev. . . family; a very late form; histopathology.] *Acta neur. psychiat. belg.* 52(3): 129–140.

BAGGIO, G. C., POZZAN, M., & SOSSAI, M. 1952. Contributo alla conoscenza delle iperostosi corticali diafisarie del lattante; sindrome di Caffey carattere familiare. [Studies on diaphyseal cortical hyperostosis in infant; familial Caffey's syndrome.] *Acta paediat. lat.* 5(5): 481–496.

BANKS, L. O., SCOTT, R. B., & SIMMONS, J. 1952. Studies in sickle cell anemia; inheritance factor, including effect of interaction of genes for sicklemia and thalassemia. *A. M. A. Am. J. Dis. Child.* 84(5): 601–608.

BARTSOKAS, S., BEYER, P., FRULHING, L., & MANTZ, J. M. 1952. L'anemic à hematies falciformes chez l'homme blanc. [Sickle cell anemia in white population.] *Arch. fr. pédiat.* 9(7): 709–710.

BAUZA, C. A., STABILE, A., & LYONNET, A. 1952. Idiocia amaurótica familiar (enfermedad de Tay-Sachs). [Familial amaurotic idiocy (Tay-Sachs disease).] *Arch. pediat. Uruguay* 23(9): 640; (10): 688–690.

BECKER, P. E. 1952. Eine klinisch-genetische Untersuchung der Dystrophia musculorum progressiva (Erb). [Clinical and genetic investigation of the progressive muscular dystrophy (Erb).] *Arch. Psychiat.*, Berl. 189(1): 1–22.

BEGG, M. 1952. Selection of a genetic basis for an acquired characteristic. *Nature*, Lond. 169(4302): 625.

BERARDINELLI, W. 1952. Hermafroditismo verdadeiro. [True hermaphroditism.] *Med. cir. farm.*, Rio 193: 185–195.

BEREDAY, M., & COBB, S. 1952. Relation of hereditary optic atrophy (leber) to the other familial degenerative diseases of central nervous system. *A. M. A. Arch. Ophth.* 48(6): 669–680.

BERREY, R., & CARSON, B. 1952. Erythroblastosis in one of dizygotic twins; a case report. *J. M. Ass. Alabama* 22(3): 79–80.

BERTOYE, P., MONNET, P., BRET, J., & TOURAINE, A. 1952. Cardiopathie congénitale chez des jumeaux dizzygotes par embryopathie. [Congenital cardiopathy in dizygotic twins; embryopathological origin.] *J. med. Lyon* 33(775): 391–393.

BIRDSELL, J. B. 1952. On various levels of objectivity in genetical anthropology. *Am. J. Phys. Anthrop.* 10(3): 355–362.

BIRO, I. 1951. Beiträge zu den ophthalmologischen Beziehungen der Blutsverwandtenehen. [Ophthalmological implications of marriage between blood relations.] *Klin. Mbl. Augenh.* 119(6): 585–596.

BOLGERT, M., CANIVET, J., & LE SOURD, M. 1952. Trois cas de porphyrie cutanée congénitale (maladie de Gunther) dans la meme fratrie. [Three cases of congenital cutaneous porphyria (Gunther Disease) in same family.] *Bull. Soc. fr. derm. syph.* 59(3): 233–236.

BÖÖK, J. A. 1952. Fréquence de mutation de la chondrodystrophie et de l'epidermolyse bulleuse dans une population du sud de la Suède. [Frequency of mutation of chondrodystrophy and epidermolysis bullosa in the south of Sweden.] *J. genet. humaine*, Geneve 1(1): 24–26.

BORNEMANN, W. 1952. Ein seltener Fall von erblicher Schneidezahnuberzahl. [A rare case of hereditary supernumerous front tooth.] *Deut. zahnärztl. Zschr.* 7(15): 879.

BROWN, R. J. K. 1952. A clinico-pathological study of cystinosis in two siblings. *Arch. Dis. Childh.*, Lond. 27(135): 428–433.

CHILDS, A. W., CROSE, R. F., & HENDERSON, P. H. 1952. Glycogen disease of the heart; a report of two cases occurring in siblings. *Pediatrics* 10(2): 208–217.

COBLENTZ, B., & MATHIVAT, A. 1952. Stenose pulmonaire congénitale chez deux soeurs. [Congenital pulmonary stenosis in two sisters.] *Arch. mal. coeur* 45(6): 490–495.

COLLIER, W. A., FROS, J., & SCHIPPER, J. F. A. 1952. Blood groups of some American Indian settlements. *Doc. med. geogr. trop.*, Amst. 4(3): 225–226.

COLLIER, W. A., PARRA, D. A. DE LA. 1952. Sickle-cell trait in Surinam creoles. *Doc. med. geogr. trop.*, Amst. 4(3): 223–224.

COMFORT, M. W., & STEINBERG, A. G. 1952. Pedigree of a family with hereditary chronic relapsing pancreatitis. *Gastroenterology* 21(1): 54–63.

CORDIER, J., LÖWENTHAL, A., RADERMECKER, M. A., & BOGAERT, L. VAN. 1952. V. Sur une forme congénitale et héréditaire de sclérose musculaire généralisée: la famille Duc. [V. A congenital hereditary form of generalized muscular sclerosis: the Duc family.] *Acta neur. psychiat. belg.* 52(5): 422–432.

CRIGLER, J. F. JR., & NAJJAR, V. A. 1952. Congenital familial nonhemolytic jaundice with kernicterus. *Pediatrics* 10(2): 169–180.

DAHR, P. 1952. Fünfzig Jahre ABO-Blutgruppensystem. [Fifty years of ABO blood group system.] *Münch. med. Wschr.* 94(18): 930–935.

DAVIDSOHN, I., LEVINE, P., & WIENER, A. S. 1952. Medicolegal application of blood grouping. *J. Am. M. Ass.* 149(7): 699–706.

DECOURT, J., & DOUMIC, J. M. 1952. Sur la fréquence et la signification des retards pubertaires familiaux. [The frequency and significance of familial cases of delayed puberty.] *Bull. Acad. nat. méd.*, Par. 136(18–19): 319–321.

DURNIN, J. V., & WEIR, J. B. 1952. Statures of university students and of their parents. *Brit. M. J.* 1(4766): 1006–1008.

ELBEL, H. 1952. Über die Genetik der menschlichen Blutgruppen. [Genetics of human blood groups.] *Deut. Zschr. gerichtl. Med.* 41(2): 186–193.

ENGLERT, E. JR., & WARSHAW, L. J. 1952. Familial mediterranean (Cooley's) anemia complicated by chronic hepatitis; results of treatment with ACTH. *Am. J. Med.* 13(4): 507–516.

EWALD, G. 1952. Fetischismus und Anlage. [Fetishism and heredity.] *Arch. Psychiat.*, Berl. 189(2): 93–108.

FADDA, F. 1952. Grupos y subgrupos del factor Rh. [Groups and subgroups of Rh factor.] *Ref. chilena pediat.* 23(1): 41–42.

FISHER, G. 1952. Tératogénèse, génétique, embryogénèse et chimiotératogénèse. [Teratogenesis, genetics, embryogenesis and chromoteratogenesis.] *Concours méd.*, Par. 74(31): 2735–2736.

FOSSEL, M., & TROJAN, R. 1951. Zur Beweiskraft der morphologische-erbbiologischen Untersuchung und Festellung der Zeugungsfähigkeit. [Morphological and hereditary factors in examination and ascertainment of testimonial capacity.] *Deut. Zschr. gerichtl. Med.* 40(5): 448–451.

FRANCESCHETTI, A., & KOENIG, H. 1952. L'importance du facteur hérédo-degeneratif dans l'hémiatrophie faciale progressive (Romberg): étude des complications oculaires dans ce syndrome. [Heredo-degenerating factor in progressive facial hemiatrophy (Romberg): study of ocular complications of this syndrome.] *J. genet. humaine*, Geneve 1(1): 27–64.

FRÖHLICH. 1952. Epidermolysis bullosa hereditaria dystrophica mit albopapuloid Erhabenheiten (Pasini) am Rumpf. [Epidermolysis bullosa hereditaria dystrophica with albopapuloid elevations on the trunk.] *Zschr. Haut & Geschlkr.* 12(3): 10–11.

GALDSTON, M., STEELE, J. M., & DOBRINER, K. 1952. Alcaptonuria and ochronosis; with a report of three patients and metabolic studies in two. *Am. J. Med.* 13(4): 432–452.

GAUTIER, P., & GUINAND-DONIOL, J. 1952. Un syndrome nouveau; la maladie de Lobstein associée à la thrombasthénie familiale et héréditaire de Glanzmann. [A new syndrome: Lobstein's disease associated with Glanzmann's familial and hereditary thrombasthenia.] *Schweiz. med. Wschr.* 82(15): 407–409.

GILG, I. 1952. Boeck's sarcoid in identical twins. *Acta derm. vener. Suppl.*, Stockh. 29: 108–115.

GRACIANSKY, P. DE, BALTER, & LEFORT, P. 1951. Xanthomes multiples chez un albinos. [Multiple xanthomas in albinos.] *Bull. Soc. fr. derm. syph.*, Par. 58(5): 479–481.

GRAY, F. G., QUINN, R. W., & QUINN, J. P. 1952. A long-term survey of rheumatic and nonrheumatic families; with particular reference to environment and heredity. *Am. J. Med.* 13(4): 400–412.

GREBE, H. 1952. Gibt es eine recessiv erbliche Chondrodysplasie (Chondrodystrophia foetalis, achondroplasie)? [Recessive hereditary chondrodysplasia (chondrodystrophy fetalis, achondroplasia).] *Zschr. Kinderh.* 71(5): 437–447.

GROVE-RASMUSSEN, M., SOUTTER, L., & LEVINE, P. 1952. A new blood subgroup (A_0) identifiable with group O serums. *Am. J. Clin. Path.* 22(12): 1157–1163.

HAVERKAMP BEGEMANN, N., & LOOKEREN CAMPAGNE, A. VAN. 1952. Homozygous form of Pelger-Huet's nuclear anomaly in man. *Acta haematol.*, Basel 7(3–4): 295–303.

HEBEL, R. 1952. Familiare Häufung der Kartagener Trias. [Familial manifestations of Kartagener's triad.] *Ztschr. Laryng.* 31(2): 83–90.

HERVE. 1951. Quelques considérations à propos du chapitre antécédents héréditaires de l'observation clinique de prothèse totale. [Remarks on the "hereditary antecedents" in the full denture case history.] *Rev. odont.*, Par. 73(12): 549–552.

HEYMAN, A., PATTERSON, J. L. JR., & DUKE, T. W. 1952. Cerebral circulation and metabolism in sickle cell and other chronic anemias, with observations on the effects of oxygen inhalation. *J. Clin. Invest.* 31(9): 824–828.

HIRZFELD, L. 1952. Über die Genetik serologischer Konflikte zwischen Mutter und Frucht. [Pathogenesis of serological incompatibility between mother and child.] *Schweiz. med. Wschr.* 82(12): 303–307.

HOLLY, P. B., FELTS, W. R. JR., & RHEINGOLD, J. J. 1952. Pernicious anemia occurring simultaneously in identical Negro twins. *A. M. A. Arch. Int. M.* 90(5): 707–710.

HUTCHESON, J. B., HABER, J. M., & KELLNER, A. 1952. A hazard of repeated blood transfusions; hemolytic reaction due to antibodies to the Duffy (Fy^a) factor. *J. Am. M. Ass.* 149(3): 274–275.

JACOBSEN, A. W., & MACKLIN, M. T. 1952. Hereditary sexual precocity; report of a family with 27 affected members. *Pediatrics* 9(6): 682–695.

JANKOVIC, B. 1952. Rh entitela i njihov klinički značaj. [Rh factors and their clinical significance.] *Srpski arh. celok. lek.* 80(1): 63–70.

KLINGMÜLLER, G. 1951. Der Morbus-Boeck in der Familie. [Familial Boeck's disease.] *Derm. Wschr.* 124(49): 1199–1204.

KNOLL, H. 1952. Wahnbildende Psychosen der Zeit des Klimakteriums und der Involution in kliniascher und genealogischer Betrachtung. [Delusion-type psychoses in the time of climax and involution; clinical and genealogical viewpoints.] *Arch. Psychiat.*, Berl. 189(1): 59–92.

KNOLL, H. A. 1952. Color vision differences in the two eyes of a given individual; a case of simulated unilateral atypical achromatopsia. *Am. J. Optometr.* 29(10): 539–542.

KRAH, E., & WILDHAGEN, K. 1952. Unspezifische Agglutinationen bei der Blutgruppenuntersuchung an menschlichen Fetalblut. [Non-specific agglutination in blood group determination of human fetal blood.] *Klin. Wschr.* 30(25–26): 610–611.

KRYNSKI, S., ARMINATE, J. C., & MILETTO, A. 1952. Anemia falciforme; considerações neuro-psiquiátricas e hematologicas a propósito de um caso. [Sickle cell anemia; neuropsychiatric and hematological considerations regarding a case.] *Hospital*, Rio 41(5): 677–700.

KULENKAMPFF, D. 1952. Uber die Behandlung des Rhinophyms und des Zungenkropfes; ein Beitrag zur Genpathologie. [Therapy of rhinophyma and the lingual goiter; their hereditary pathology.] *Chirurg.* 23(9): 405–410.

KUPPERMAN, H. G., & BARTFELD, H. 1952. Rheumatoid spondylitis treated with cortisone; heredity and effect on pregnancy. *N. Y. State J. M.* 52(9): 1157–1159.

LEHMANN, W. 1952. Das erbbiologische Gutachten. [Hereditary evaluation of paternity.] *Deut. Zschr. gerichtl. Med.* 41(2): 173–185.

LOWENTHAL, A. 1952. Etude sur les myosites. IV. Sur une forme congénitale et familiale de sclérose musculaire généralisee avec blépharoptose (contribution a l'etude des maladies congénitales des muscles et du tissu conjonctif). [Myositis. IV. Congenital and familial form of generalized muscular sclerosis with blepharoptosis (contribution to the study of congenital diseases of muscles and connective tissue).] *Acta neur. psychiat. belg.* 52(3): 141–155.

MCEVITT, W. G. 1952. Cleft lip and palate and parental age; a statistical study of etiology. *Plastic & Reconstr. Surg.* 10(2): 77–82.

MACMAHON, B., & MCKEOWN, T. 1952. A note on the sex ratio in anencephalus. *Brit. J. Social M.* 6(4): 265–266.

MAGGIORE, L. 1952. I matrimoni fra consanguinei: pericoli per la integrità dei discendenti; l'importanza ed il significato dei fattore consanguineità dei genitori nella genesi di talune forme morbose ereditaire dell'apparanto visivo. [Consanguinity in marriage as a hazard for children; importance and significance of consanguinity in hereditary diseases of the visual apparatus in children.] *Athena*, Roma 18(7–8): 303–305.

MERTINS, H. 1952. Uber eine familiäre Zwerchfellmissbildung. [Familial abnormality of the diaphragm.] *Zbl. Gyn.* 74(24): 951–955.

METELKA, J. 1952. Osteopoikilie (osteopetrosis Albers-Schonberg II.) ve třech generacích. [Osteopoikilosis (Albers-Schonberg's osteopetrosis) in three generations.] *Lék. listy*, Brno 7(18): 458–461.

MOLLA, W. 1952. Comportamento dell'antigene A nei gruppi AB. Antigen A in blood groups AB. *Sangue*, Milano 25(1): 4–13.

MØLLER, P. M. 1951. Another family with von Hippel-Lindau's disease. *Acta ophth.*, Kbh. 30(1): 154–165.

MOORRESS, C. F. A., OSBORNE, R. H., & WILD, E. 1952. Torus mandibularis: its occurrence in Aleut children and its genetic determinants. *Am. J. Phys. Anthrop.* 10(3): 319–320.

MORTELMANS, L. 1952. Forme familiale de la dystrophie cornéenne de Fuchs. [Familial form of Fuch's corneal dystrophy.] *Ophthalmologica* 123(2): 88–99.

MULLER, H. J. 1951. Strahlenschädigung des genetischen Materials. [Radiation injuries of the genetic material.] *Strahlentherapie* 85(4): 509–536.

MUTRUX, S. 1951. Etude d'un cas familial de paralysie pseudo-bulbaire a forme pontocérébelleuse. [Study of a familial case of pseudobulbar paralysis of the pontocerebellar type.] *Mschr. Psychiat.*, Basel 112(6): 349–384.

NAYRAC, P., HOUCKE, E., BISERTE, G., & RABACHE, R. 1951. Dégénérescence hépatolenticulaire chez la soeur et le frère; ponction-biopsie du foie; amino-acidurie. [Hepatolenticular degeneration in brother and sister; liver puncture biopsy, amino-aciduria.] *Rev. neur.*, Par. 85(5): 388–392.

PEQUINGNOT, H. 1952. Un code d'eugénique en Finlande. [Eugenic code in Finland.] *Sem. méd.*, Par. 28(1): 1–2.

PFÄNDLER, U. 1952. La transmission combinée dans une même souche de trois maladies héréditaires différentes (ostéochondrose déformante juvénile de la hanche, hypoplasie du femur, dystrophie musculaire progressive. [Combined transmission of three different hereditary diseases in the same family (deforming juvenile osteochondrosis of the hip, hypoplasia of the femur, progressive muscular dystrophy.] *J. genet. humaine*, Geneve 1(1): 56–82.

PFÄNDLER, U. 1952. La voie de la Génetique du Micromérisme a l'Atomisme biologique. [Development in genetics; from micromerism to the biological atomic theory.] *Schweiz. med. Wschr.* 82(10): 258–260.

PHANSOMBOON, S., & POLLAK, O. J. 1952. A study on the A factor as a cause of haemolytic disease in premature babies. *Brit. M. J.* 1(4769): 1170–1172.

PHILIPP, E. E., & SKELTON, M. O. 1952. Congenital diaphragmatic hernia in siblings. *Brit. M. J.* 1(4771): 1283–1284.

PORTIER, A., & MASSONNAT, J. 1952. Epilepsie et syndrome hematologique méditérranéen. [Epilepsy and the Mediterranean hematological syndrome.] *Presse méd.* 60(19): 395–396.

PROCHAZKA, J. 1952. Vrozené kyčelní dysplasie u trojčat. [Congenital hip dysplasia in triplets.] *Acta chir. orthop. traum. čech.* 19(4–8): 245–251.

PROPPE, A. 1952. Geschlechtsgebundene Dermatosen. [Skin diseases transmitted by the sex genes.] *Zschr. Haut & Geschlkr.* 13(6): 166–174.

PUIGGROS SALA, J. 1951. Contribución a la histologia de la eritroblastosis por factor Rh. [Contribution to the histology of erythroblastosis due to the Rh factor.] *Arch. espań. morf.* 9(32): 83–90.

RABASA, S. L. 1951. Base genética de algunas enfermedades de la sangre. [Genetic basis in certain blood diseases.] *Pediat. Amer.*, Mex. 9(8): 343–353.

RAPP, G. W., & RICHARDSON, G. C. 1952. A saliva test for prenatal sex determination. *Science* 115(2984): 265.

REILLY, E. B., RAPAPORT, S. I., KARR, N. W., MILLS, H., & CARPENTER, G. E. 1952. Familial chronic lymphatic leukemia. *A. M. A. Arch. Int. M.* 90(1): 87–89.

RISETTI, U., & PROPERZI, E. 1952. Infantilo-nanismo diencefalo-ipofisario atipico con carattere familiare, aracnodattilia e malformazioni multiple. [Atypic diencephalo-hypophyseal infantile-nanism with familial characteristics; arachnodactyly and multiple malformations.] *Fol. endocr.*, Pisa 5(1): 77–106.

ROBERTS, M. H., & BAEHREN, P. F. 1952. Adrenocortical insufficiency observed in three male infants in one family. *J. M. Ass. Georgia* 41(7): 299–304.

ROCHA, J. M. D., & CASTRO, A. S. D. 1952. Enfermededes sanguineas de tendencia hemorragipara; sindromos hemorragiparos familiares. [Familial hemorrhagic syndromes.] *Arch. pediàt. Uruguay* 23(10): 704–706.

ROLLINS, W. C., & COLE, H. H. 1952. The relative importance of genetic and environmental factors in determining the precision of gonadotrophin assay. *Endocrinology* 51(3): 203–209.

ROUSSET, J. 1952. Génodermatose difficilement classable (trichorrhexis nodosa) prédominant chez les mâles dans quatre générations. [Genodermatosis of difficult classification (trichorrhexis nodosa) predominant in males in four generations.] *Bull. Soc. fr. derm. syph.* 59(3): 298–300.

RUEDEMANN, A. D. JR. 1953. Osteogenesis imperfecta congenita and blue sclerotics; a clinicopathological study. *A. M. A. Arch. Ophth.* 49(1): 6–16.

SANGUINETI, I. 1950. Contributo allo studio delle sindromi distrofiche eredo-familiari; su un caso di associazione dell'amiotrofia tipe Charcot-Marie con il morbodi Friedreich. [Contribution to the study of heredo-familial dystrophic syndrome; case of the association of Charcot-Marie amyotrophia with Friedreich's disease.] *Sistema nerv.* 2(2): 141–144.

SCHACHTER, M. 1950. Syndrome Schizophreniforme et oligophrenique infantile, précose, role des facteurs constitutionnels, gestatifs et post-nataux. [Early infantile schizophrenia and oligophrenic syndrome; role of constitutional, pregnancy and post natal factors.] *Sistema nerv.* 2(2): 87–92.

SCHAFFER, R. C. 1952. Familial colonic polyposis; review of the literature and report of four cases. *Am. J. Surg.* 84(4): 477–482.

SCHILLING, V. 1952. Die juristische Bedeutung der Pelger-Huëtschen Kernanomalie der Leukocyten. [Legal importance of Pelger-Huet nuclear abnormality of the leukocytes.] *Med. Klin.*, Berl. 47(26): 861-864.

SCHOCKAERT, R., & JANSSENS, J. 1951. Hydrocéphalies congénitales répétées. [Repeated congenital hydrocephalus.] *Bull. Fĕd. soc. gyn. obst. fr.* 3(4): 560–566.

SCHWARTZ, M. 1952. Heredity in bronchial asthma; a clinical and genetic study of 191 asthma probands and 50 probands with Baker's asthma. *Acta allerg. Suppl.*, Kbh. 2: 1–288.

SCHWARZ, G. A. 1952. Hereditary (familial) spastic paraplegia. *A. M. A. Arch. Ner. Psychiat.* 68(5): 655–662.

SELBY, E. R. 1952. Hereditary transmission of physical defects in the EMB family. *Canad M. Ass. J.* 66(5): 439–441.

SIOLI, G. 1952. Beitrag zur Kasuistik und Erbbiologie der spatischen Spinalparalyse. [Case reports and hereditary biology of spastic spinal paralysis.] *Nervenarzt.* 23(6): 220–222.

SOVIK, W. E. 1952. Bilateral retinoblastoma in six siblings. *Am. J. Ophth.* 35(11): 1611–1618.

STOBBE, H., & TAESCHNER, H. 1952. Konkordantes Auftreten lymphatischer Leukämie bei eineiigen zwillingen; Beitrag zur familiären Leukose. [Concordant appearance of lymphatic leucemia in identical twins.] *Zschr. ges. Inn. Med.* 7(16): 736–739.

TESORO, J. 1952. Los factores Rh sanguineos. [Rh blood factors.] *Dia méd.*, B. Air. 24(10): 200–204.

THORSEN, H. U. 1952. Et tilfelle av odontogenesis imperfekta hereditaria. [A case of hereditary odontogenesis imperfecta.] *Norske tannlaegeforen. tid.* 62(1): 67–71.

TOGERSEN, J. 1952. The Triad of Kartagener; a contribution to its hereditary and developmental basis. *Schweiz. med. Wschr.* 82(30): 770–771.

TOURAINE, A. 1952. Les états héréditaires d'atrophies cutanées avec sénescence prematurie; syndromes de Rothmund, de Werner, poikilodermie congenitale de Thomson, myotonie atrophique de Steinert, progeria, acrogeria, etc.; nouvelle chaine héréditaire. [Hereditary status of cutaneous atrophy with premature senescence; Rothmund's syndrome, Werner's syndrome, Thomson's congenital poikiloderma, Steinert's atrophic myotonia, progeria, acrogeria, etc.; new hereditary chain.] *Ann. derm. syph.*, Par. 79(4): 446–451.

TOURAINE, A. 1952. Utilité de publier de nombreuses observations de génétique médicale. [Value of publishing numerous observations on medical genetics.] *Gaz. méd. port.* 5(1): 91–95.

TRAMPUZ, V. 1952. Fetomaterna krvna inkompatibilinost po sistemu-ABO. [Feto-maternal blood incompatibility in ABO group.] *Zdrav. vest.*, Ljubljana 21(3–4): 54–57.

TRINCÃO, C., SOARES, A. D., LANCA, J. B., & FLORA, A. 1952. Ictericia não hemolitica familiar. [Familial non-hemolytic jaundice.] *Gaz. méd. port.* 5(3): 339–348.

TUCHMANN-DUPLESSIS, H. 1952. Les bases expérimentales de déterminisme et de la différenciation sexuelle. II. Vertébrés. [The experimental bases for sex determination and differentiation. II. The Vertebrates.] *Concours méd.*, Par. 74(21): 1973–1975.

TUCHMANN-DUPLESSIS, H. 1952. L'hérédite pathologique. [Pathological heredity.] *Concours méd.*, Par. 74(28): 2561–2564.

TURPIN, R., SENECAL, J., & SCHÜTZENBERGER, M. P. 1952. Consanguinité et tuberculose. [Consanguinity and tuberculosis.] *Bull. Acad. nat. med.*, Par. 136(1–2): 10–12.

VAN BOGAERT, L. 1952. Etude génétique sur les paraplégies spasmodiques familiales. [Genetic study of familial spasmodic paraplegia.] *J. genet. humaine*, Geneve 1(1): 6–23.

VAN GEERTRUYDEN, E. 1952. Premiere observation belge de la malformation congénitale de Ullrich-Bonnevie. [The first Belgian observation of the Ullrich-Bonnevie malformation.] *Acta neur. psychiat. belg.* 52(2): 102–110.

VAUGHAN, V. C. III, ALLEN, F. H. JR., & DIAMOND, L. K. 1952. Variability in erythroblastosis fetalis: a study of multiple pregnancies and of twins. *A. M. A. Am. J. Dis. Child.* 84(6): 739–740.

VERSCHUER, O. VON. 1952. Erbforschung am Menschen-neure Ergebnisse und Erkenntnisse. [New results of human genetics.] *Deut. med. Wschr.* 77(41): 1245–1248.

VOLPE, A., RAMON GUERRA, A. U., ESCADE, C. A., & BOCCOLERI, C. S. 1952. Síndromo de anemia aplasica (panhematopenia) familiar asociado a hypocrecimiento y diabetes renal. [Syndrome of familial aplastic anemia (panhematopenia) associated with retarded growth and renal diabetes.] *Arch. pediat. Uruguay* 23(10): 715–716.

WAARDENBURG, P. J. 1952. Angio-sclerose familiale de la choroide. [Familial angiosclerosis of the choroid.] *J. genet. humaine*, Geneve 1(1): 83–90.

WADDINGTON, C. H. 1952. Selection of the genetic basis for an acquired characteristic. *Nature*, Lond. 169(4302): 625–626.

WADE, G. 1952. Congenital heart disease in one of uniovular twins. *Brit. Heart J.* 14(4): 475–480.

WEISS, A. 1952. Blutdruck und erbleiche Lebenserwartung. [Blood pressure and hereditary life expectancy.] *Arch. Kreislaufforsch.* 18(7–10): 301–322.

WHITTEN, W. W., & ADIE, G. C. 1952. Congenital biliary atresia; report of three cases; two occurring in one family. *J. Pediat.*, S. Louis 40(5): 539–548.

WILDHAGEN, K., & KRAH, E. 1952. Zur Frage der embryonalen Entwicklung der Blutgruppenmerkmale beim Menschen. [The embryonic development of blood groups in man.] *Geburtsh. & Frauenh.* 12(8): 744–757.

WILLIAMS, D. I. 1952. The diagnosis of intersex. *Brit. M. J.* 1(4771): 1264–1270.

ZUNIN, C. 1951. Contributo alla conoscenza dello status Bonnevie-Ullrich. [Studies on Bonnevie-Ullrich.] *Minerva pediat.*, Tor. 3(10): 547–557.